KETTLE'S PATHOLOGY OF TUMOURS

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PREFACE TO THE THIRD EDITION

KETTLE'S Pathology of Tumours occupied a unique place among text-books of Pathology. It was essentially personal in its approach and presentation. The illustrations were drawn by Kettle and had exactly the right emphasis to show clearly the points he described. Kettle believed that "all cancer research must ultimately rest on a histological basis" and that "it is of the greatest importance to correlate with human pathology the results of experimental research But for any work along these lines to be fruitful it is essential that it should rest upon a sure foundation of wide and accurate knowledge"

These beliefs coloured the presentation and his own wide knowledge informed the matter of the book. His plan was "to provide a manual for students which should contain the generally accepted teaching on the pathology of tumours without the mass of detail proper in a more ambitious work of reference."

In the years that have passed since the publication of the second edition great advances have been made both in the experimental and in the detailed histological studies of tumours. We have included those we think most likely to form permanent additions to knowledge and at the same time have tried to preserve as much as possible the character and happy phraseology of the earlier editions

We humbly dedicate this edition to the memory of a great teacher and valued friend and if as a result of its publication, Kettle's name is kept fresh in the minds of students of Pathology we shall consider our efforts amply repaid We gratefully acknowledge our indebtedness to help freely given by Drs. W. E Gye, B D Pullinger, D. S Russell and many others.

W. G. B.
A H. T. R -S.

Both authors share responsibility for Parts II and III but for Part I W. G Barnard is alone responsible

PREFACE TO FIRST EDITION

In the following pages I have tried to present as briefly as possible the chief points bearing on the general and special pathology of Neoplasms. My aim has been to follow the generally accepted teaching, and I have, therefore, availed myself freely of the standard text-books on the subject, as well as special monographs and articles in the various scientific journals; but I have purposely refrained from giving references to the literature, except in a few instances where it appeared advantageous to do so.

Considerations of space have led me to omit descriptions of technique, and this I do not regret, since there is nothing peculiar to the histological examination of tumours, and the ordinary laboratory procedures should be familiar to the student who proposes to undertake a practical study of the subject.

The illustrations have been specially prepared for this book from cases which, with one or two exceptions, have come under my own observation, and I have relied chiefly on figures drawn from microscopic preparations, for those depicting macroscopic specimens are rarely sufficiently distinctive to be of any great value.

E. H. KETTLE

London, 1916.

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PART I

THE GENERAL BIOLOGY OF TUMOURS

DEFINITION

IN medicine, as a result of greater knowledge, words which were originally used in a wide and general sense are used in an increasingly restricted sense until finally their use implies a particular and well-defined condition.

This limitation is well illustrated in the use of the word tumour. Originally it was used for any lump; now it implies a lump of a particular kind. Tumours are composed of masses of newly formed cells arising from native body cells and usually bearing some recognisable resemblance to their parent cells. Their cells continue to divide and the tumour continues to grow to an extent limited only by the life of the individual. In spite of all this activity the tumour never reaches a natural destination, it achieves no goal, often it is most active at the time of the death of the patient. Its growth is unlimited, progressive, purposeless and uncontrolled. In repair cells proliferate, in response to work they may hypertrophy, in regeneration they multiply; but when these things happen their activities conform to what is known of normal cell behaviour. They contribute more or less effectively to the functional activity of the tissue or organ of which they form a part. In tumours the cells no longer behave as normal cells, their growth and activity appear to be independent of the laws co-ordinating the growth and activity of the tissue or organ in which they arise. There is no evidence that this autonomy is due to change in the neighbouring tissue or cells so that it appears certain that the change is in the cells themselves. As we are certainly ignorant of the essential ætiological factor responsible for this change in cell behaviour, there is no satisfactory definition of a tumour. The simplest and least unsatisfactory is that a **tumour is an autonomous new growth.**

The other attributes of most tumours are not necessarily peculiar to tumour growth. Unlimited potentiality for growth is not confined to tumour cells. In tissue culture chick fibroblasts can be grown by continuous subculture for a number of years far exceeding the expectation of life of a fowl. If returned to a chicken, they behave as normal fibroblasts and do not exhibit any of the signs of a tumour. There is, however, a difference between normal cell proliferation in the body

and the proliferation of cells of tumours , in the normal, the stimulation to proliferate appears to come from without the cell, in tumours the stimulus appears to be within the cell itself.

Some tumours produce secretions such as mucus and others secretions which show their activity by bringing about changes in the body, thus clearly demonstrating that all tumours are not functionless. That tumours subserve no useful purpose is more generally true, but there are rare exceptions even to this. Autonomy is the feature which is peculiar to all tumours and which explains their peculiarities in growth and behaviour.

Until conclusive evidence to the contrary is forthcoming it must be accepted as a fundamental rule that there are no tissues in the body exempt from tumour formation. There is no justification for such statements as " tumours do not arise in " ; if they are made they should be interpreted in the sense that the authors of the statement have no knowledge of such tumours and not that the tumours do not in fact arise in the tissue described.

It might appear from this general introduction that there will be no difficulty in identifying a tumour, and this is true for the majority of tumours. But in some few instances there is no sharp separation between granulomatous inflammations and tumours and between hyperplasias and tumours. Once a tumour has fully declared itself there is little difficulty in its recognition, but there are a number of conditions which we know by experience are associated with tumour production and in some of these it is sometimes a matter of great difficulty or even impossibility to say whether they have in fact become tumorous.

STRUCTURE

Structure of Tumours. All tumours are derived from pre-existing cells of the body and resemble them more or less closely. In some cases the resemblance is so close that the source of origin is never for a moment in doubt , on the other hand, the histology of the growth may differ so widely from the normal that it is only after careful study of a series of such growths that we are able to decide on the parent tissue. The former class are known as **typical**, and the latter as **atypical.**

Tumours consist of two parts, a connective tissue matrix or stroma, and the parenchyma or tumour cells proper : it is the latter portion which gives the tumour its distinctive character. The relationship between stroma and parenchyma varies very considerably in different growths, or even in different portions of the same growth. In those

of the epithelial or glandular type the two constituents are easily distinguishable, and the stroma may be more abundant than the parenchymatous element, but in the connective tissue group the reverse holds good, and it may be quite difficult to demonstrate any matrix whatever.

Parenchyma. Speaking generally, the innocent growths are typical, and the parenchyma cells bear a strong likeness to the normal cells of the tissue from which the tumour arose. So close is this likeness that it is only by a study of the arrangement of the cells that we are able to distinguish the neoplastic nature of the condition. In malignant tumours, on the other hand, the cells differ considerably from their normal prototypes; that is to say, malignant growths are atypical, and their cells frequently fail to attain maturity, continuing to divide while still in an immature form, so that it may be difficult, if not impossible, to determine their origin. Not only are the individual cells atypical, but their arrangement or relationship to one another varies widely from the normal, and they are peculiarly liable to degenerative processes

Between these extremes all grades may exist, giving rise to the various types of tumour which we have to study.

Similar differences are seen in the physiology of tumours and may be reflected in their histology. Those of the innocent type often retain some of the functions of the tissue from which they originated. Thus, an adenoma of mucus secreting epithelium tends to produce mucus, though the production is imperfect or perverted; tumours of the thyroid gland commonly contain colloid; liver tumours may form bile; while in growths of osteogenetic tissue the formation of true bone may occur. In malignant tumours such behaviour is, at the best, imperfect and is usually absent. While some do, many carcinomata of the rectum produce little or no mucus; an osteosarcoma contains osteoid tissue rather than true bone, and so forth.

Very important changes occur in the nuclei of the parenchyma cells In the typical growths the nuclei are more or less normal, but the atypical forms may present profound variations these consist of alteration in size and shape, multiplications, degenerations, and pathological forms of division. In the older parts of the tumour the nuclei may be shrunken and distorted, deficient in chromatin (chromatolysis), or fragmented (karyorrhexis). At the growing margin the nuclei may show great variations in size, both from the normal and from each other, while cells containing two or more nuclei may be encountered, and, indeed, are characteristic of certain forms of tumour.

Irregularities in mitoses are common. There may be a diminished number of chromosomes (hypochromatic mitosis), or an increased number (hyperchromatic mitosis); the mitosis may be asymmetrical, and, resulting from an excess of centrosomes, we may encounter pluripolar forms. In spite of these changes it is important to emphasise that although the cells of a malignant tumour may be atypical, no constant feature has yet been recognised by which an isolated cancer cell can be identified.

Stroma. The stroma of a tumour is derived from the connective tissues of the organ in which it is growing and is necessary for the growth and development of the tumour cells. It has been suggested that when it is excessive in amount it might choke the tumour cells and give rise to real or practical cure But in the vast majority of cases it is merely sufficient to support the parenchyma cells and provide them with nourishment. Here we may note that this stroma reaction is vital to the life of the neoplasm; if the tissues of the host do not react, providing a framework with nutrient vessels for the parenchyma, the tumour is unable to live.

It is in the innocent group that the essential nature of the stroma is most obvious, for here stroma and parenchyma grow side by side, the one increasing with the other. In the malignant growth, on the other hand, the parenchyma invades and absorbs surrounding tissues, thus constantly adding to its stroma by this means as well as by a fresh formation.

In some tumours the parenchyma has a powerful influence in determining the nature of the stroma. Thus, the framework may be extremely meagre in amount, consisting chiefly of capillary blood vessels with an occasional delicate meshwork of collagenous fibrils, or it may be abundant and composed of dense fibrous tissue; or it may undergo various changes such as calcareous degeneration; or it may even be stimulated to undergo a neoplastic change itself.

It is obvious that, in order to live, a new growth must receive nourishment and must also be provided with drainage in the form of lymphatics to remove its metabolic products These are supplied by the stroma.

In innocent tumours the blood vessels are, as a rule, fairly well developed, but in the malignant group they are often less differentiated, consisting for the most part of capillaries or sinuses, and often lying in direct continuity with the tumour cells

Occasionally one may encounter formed vessels in the substance of a malignant growth; but these are generally the vessels of the tissue

which has been invaded, and they often exhibit a varying amount of endarteritis.

Tumours themselves are devoid of sensation, and, as we should expect, few nerves are present in them. A malignant growth may envelop the nerves of the tissues it is invading, but these are limited to the periphery, and few are present in the substance of the growth.

GROWTH

In all tissues and organs of the body a fine balance is maintained between the supporting tissues, blood supply and the functioning tissue. And in the body as a whole the organs are maintained at a constant optimum. This optimum varies for each organ, but it always insures a considerable reserve. The kidneys, for instance, provide a reserve of about four times the actual requirement to maintain life. Further, in all these organs, if part of them is lost the remaining part will attempt by hypertrophy or hyperplasia to make good the loss. This clearly shows that the power to grow is present but is not exercised unless there is some interference with the normal balance between the organs With such a tissue as blood, experiments can be designed to provide a body with an excess, but this also is not tolerated. The optimum is maintained by all possible means, but neither more nor less than the optimum. These things we know, but the means by which these laws are maintained in the body we do not know. A difference between this normal maintenance and tumorous growth is that in the normal there appears to be some sort of relationship between the body as a whole and the local growth, whereas in tumours no such relationship exists.

Under normal conditions the products of autolysis of cells in the body provide a stimulant to tissue growth. This is a perfectly balanced mechanism by which the stimulus is exactly proportional to the amount of tissue destruction and therefore to the amount of cell proliferation required to make good the damaged tissue. The constitution of these normal growth stimulants is unknown. Something of the same kind is demonstrated in tissue culture where for perpetual growth it is necessary to add embryo extract to the culture medium.

It is impossible to trace the actual origin of tumour cells, because the preparations available for microscopic study consist of fixed tissues and in these, transition from normal to tumorous can only be surmised —it cannot be seen. The earliest tumours are already formed if we can recognise them and if not they are not yet tumours.

It is, however, generally believed that tumours arise from one cell, a

small group of cells, or a few cells which soon join to form a single mass of cells All the subsequent mass of tumour cells are direct lineal *descendants of these first cells which became tumorous.* That is to say that tumours grow by multiplication of their cells and not by the addition of neighbouring cells which have also become tumorous. This is possibly not an absolute rule, as in the neighbourhood of carcinoma in tongue and colon there are *often changes in nearby cells* suggestive of malignancy. So far it has been impossible to prove whether this represents a transformation of normal cells to malignant, or a peculiar spread of malignant cells so that they occupy the place of, and are mixed with, normal cells. At present it is advisable to regard most tumours as being of unicentric and not multicentric origin.

The cells of the body vary within wide limits in their ability to proliferate. We depend on the proliferation of white fibrous tissue to form the internal or surface scars which throughout life represent the healed stage of wounds and most inflammations. The cells of the blood and of the epithelia covering surfaces are constantly being lost and renewed. Other cells, like those of the breast and endometrium, have cycles of change and in response to special stimuli have great powers of proliferation. Those cells which are well trained in proliferation and which respond readily to stimuli to proliferate are the cells which most commonly give rise to tumours. It should be noted that this generalisation applies to the cells and not only to the tissue or organs. So that in any given tissue or organ the cells *most likely to give rise to a tumour* will be those cells which most readily proliferate. It is unlikely that senile cells multiply, but at what degree of maturity they lose this power is uncertain. The epithelium of the skin is constantly being renewed *from a germinal layer in its depths* and its external layers constantly lost. The germinal layer is practised in proliferation ; the cells produced mature until they form part of the prickle cell layer and then gradually become effete until they are fused in the horny layer. The most likely source of all tumours of skin epithelium is this germinal layer. The differences in histological appearances and behaviour are differences in the degree of maturity reached by the cells of the tumour.

When a normal cell undergoes division it does not immediately produce two fully matured cells. First the two cells are immature, more or less spherical, oval or polygonal, and later they mature and assume the characters of an adult cell These first indifferent cells are also produced in tumours, but in these the cells may :

(*a*) Continue to multiply without any of them attaining maturity (anaplasia) ,

(*b*) pass through all or only some of the stages of maturing cells of the tissue from which they have arisen, or

(*c*) Mature in a manner unlike that of the parent tissue (metaplasia).

The rate of growth varies very considerably in different types of tumour, and even in the same example from one interval of time to another. For the most part the typical tumours grow slowly and the atypical forms rapidly. Both varieties, but especially the atypical, are subject to sudden exacerbations, and, as has been demonstrated in the studies of the Imperial Cancer Research Fund, propagable malignant tumours show a constant cycle of waxing and waning growth.

The mode of growth is of importance, and differs in the two main varieties. In the typical forms the increase of substance is uniform, or tends to be so, throughout the whole mass; but in the atypical forms peripheral extension is the rule, with little or no growth in the central parts. In other words, the increase of size is by **expansion** in the one form and by **infiltration** in the other, and, as we shall see, this difference plays a dominating part in the life-history of the growth.

In man the growth of a tumour is to a large extent independent of the physical condition of the host. However emaciated the host may be, the tumour itself is well nourished and makes the first claim upon such resources as remain to be drawn upon. This is also seen in experimental animals fed on a diet deficient in tryptophane, a substance which is essential for life and must be supplied in the food since it cannot be synthesised in the body. In such animals Cramer [1] has shown that transplanted tumours grow as readily as in the normal controls, but the onset of the fatal symptoms of this deficiency disease is definitely hastened by the presence of the growing tumour. In other words, the tumour demands and receives from its host such small quantities of tryptophane as may be available, though the life of the animal is sacrificed thereby. In some animal experiments diet appears to influence the development of cancer while in other experiments no influence can be detected.

On the assumption that they are necessary for growth, it has been suggested that the absence of **vitamins** from the diet might influence adversely the growth of tumours, and the treatment of cancer has actually been attempted along these lines It has been shown experimentally, however, that the rate of growth of tumours in animals fed on a vitamin-free diet does not differ materially from that seen in control animals on a normal diet; nor does an excess of vitamins

[1] *Eighth Scientific Report, Imperial Cancer Research Fund*, 1923, 17.

constantly find the cells of the growth secreting mucus. In the more malignant tumours of this region, however, the cells change in type, the cytoplasm diminishes in amount, the nuclei are relatively larger than normal, goblet cells may be absent, acini are irregularly formed, and there may be little or no attempt at the production of mucus (Fig. 1). In other forms of carcinoma of colon or rectum there is well-marked secretion of mucus which may be sufficient to give the growth a glairy naked-eye appearance. "*Colloid*" carcinoma is of this type. There is no essential difference between the secretion of mucus in these growths and its normal physiological counterpart.

In carcinomas of the thyroid, both in the primary tumour and in the metastatic deposits, the growth in certain instances appears to produce colloid, and carcinomas of the liver, especially the more innocent forms, produce bile (Fig. 2); but in spite of these and other examples we find that, as a general rule, the cells of malignant tumours lose their physiological function and devote themselves entirely to growth.

A variable degree of anaplasia, then, is the rule in malignancy, but too much reliance must not be placed upon it as a diagnostic sign. It cannot be too strongly emphasised that it is impossible to recognise an isolated cancer cell as such; it is only by a consideration of the histological structure of the tumour as a whole that we are able to arrive at a diagnosis.

(*c*) **Infiltration.** As has been pointed out in the section on growth, an innocent tumour increases in mass uniformly, compressing the surrounding tissues to form a pseudocapsule. There is a certain amount of reaction on the part of the tissue adjacent to the growth, resulting in the formation of a loose zone of areolar inflammatory tissue which is easily torn through, making the apparent encapsulation more obvious, and permitting of the familiar process of "shelling out." In malignant tumours, on the other hand, the growth is mainly peripheral, and there is little compression or pushing aside of the adjacent tissues; but there is an active invasion on the part of the peripheral cells of the tumour, which insinuate themselves between muscle fibres, into tissue spaces, lymphatics, and blood vessels. This infiltrative growth is by no means always obvious to the naked eye, and a small malignant tumour growing in loose areolar tissue, or a yielding organ such as the lung, may appear to be encapsulated Thus, in the experimental study of cancer where propagation is secured by the inoculation of small fragments of tumour into the loose areolar tissue under the skin, the resulting tumour is commonly of rounded form and apparently not adherent to skin or body wall; yet eventually it becomes fixed, and metastases develop.

FIG 1 Rapidly growing carcinoma of rectum stained with hæmatoxylin and muci carmine The normal epithelium to the left of the figure takes the carmine stain, but very little mucin is formed by the malignant cells

Zeiss obj aa Comp oc 4 Tube length, 160 mm.

FIG 2 Slowly growing liver-cell carcinoma stained with hæmatoxylin In their form and arrangement the malignant cells closely resemble the normal, and there is a plentiful secretion of bile (stained green)

Obj 8 mm. apochrom Comp. oc. 4. Tube length, 160 mm.

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In other words, as long as a tumour has room to grow and expand it will do so without the destruction of tissue, only when confined and compressed does it exert its infiltrative properties. From anatomical considerations, however, it is obvious that a human malignant growth can only maintain its footing by the destruction of healthy tissue, and accordingly we always find infiltration in progress at the margin of any considerable growth. Microscopically, infiltration is perhaps the most important sign in the diagnosis of malignancy. When present, it enables us to diagnose the condition from the examination of a single preparation without any further knowledge of the case.

(*d*) **Formation of Metastases and Local Recurrence after Removal.** Although there have been recorded instances of otherwise innocent tumours which have formed metastases, these cases are so excessively rare that the production of a metastatic tumour must be considered an unequivocal sign of malignancy.

By the term metastasis we mean the formation at a distance from the original tumour of a secondary tumour having similar characteristics to the primary one, and obviously derived from it. The question of secondary growths is one of very great importance and will be dealt with in detail later; it is sufficient for the present to note that they occur eventually in the life of practically every malignant tumour, that they vary in size and number within very wide limits, and that they may appear early or late in the course of the disease. From what has been said in the preceding section with regard to encapsulation and infiltration, it is clear that the boundaries of a malignant tumour are widespread and ill-defined, and this is the explanation of the fact that such growths are peculiarly liable to recur after removal. It is common knowledge that a wide margin of healthy tissue must be included in the removal of any malignant tumour if there is to be any hope of a permanent cure, whereas an innocent growth may be "shelled out" of its capsule with no anxiety as to its recurrence. However, there are numerous exceptions to this rule. Malignant growths are constantly removed with perfect success; were it not so, the disease would be even more terrifying than it is, and, contrariwise, local recurrence may, and does, occur after the removal of a perfectly innocent growth. This may be due to the fact that, owing to local anatomical conditions, the tumour grows unequally, forming outlying lobules often attached to the parent growth by fragile connections, these may be torn through in removal, leaving a remnant to continue its growth. By the examination of large sections, including the greatest diameter, of fibro-adenomata of the breast, Cheatle has been able to demonstrate the presence of such

subsidiary nodules within, or without, the capsule of many of these tumours.

Another source of the apparent recurrence of innocent tumours may be found in the occurrence of multiple tumours, one or more of which may have escaped observation at the time of operation. Multiple fibro-adenomata of the mammæ are frequently observed. While in other breasts showing adenomatous hyperplasia with cyst formation (chronic mastitis) some of the cysts may contain papillomata and these too may be multiple. They may be too small to detect naked eye and, following partial removal of a mammary gland, may continue to grow and so appear to be recurrences.

(*e*) **Ulceration.** As a diagnostic sign, ulceration is of little value; it is frequently absent in malignant tumours and may be present in innocent ones, though in the latter case the tumour has usually attained a much greater size than in the former. In the case of non-malignant neoplasms ulceration will take place when the covering skin or mucous membrane is stretched by the mass of the growth, or when it is exposed to injury; and, in point of fact, both factors are usually present. In malignant neoplasms not only are the mechanical factors concerned, but there is usually a direct invasion and destruction of the tissues by the malignant cells.

(*f*) **Tendency to Central Degenerative Changes.** Here again we have a sign which is of comparatively little importance, though it may indicate a considerable rapidity of growth. We have seen that a malignant growth obtains its nourishment from the new-formed vessels of the stroma supplied by the host, and it is easily understood that such a stroma requires a certain amount of time for its formation. Should the tumour be a very rapidly growing one, the stroma will be imperfect, and there will be an indifferent blood supply to the central part, with the result that necrosis of tissue will occur.

But degenerative changes other than necrosis may occur, and in tumours of a low grade of malignancy. Thus, myxomatous degeneration of a fibrosarcoma is of frequent occurrence and may be so advanced as to affect the greater part of the tumour, converting it into a mass of jelly-like consistence enclosed in a thin shell of tissue, though it is common knowledge that such tumours are not of a highly malignant nature.

(*g*) **Occurrence of Cachexia and Anæmia.** In most advanced cases of malignant disease, and occasionally in quite early cases, the patient loses strength, becomes very emaciated, and presents a peculiar yellowish appearance of the skin; and there is usually a more or less

advanced degree of anæmia. It is to this syndrome that the name cachexia is given, and it has been a matter of some debate as to whether the symptoms are due to the presence of the malignant growth or not. In tumours of the alimentary tract where there is direct or indirect interference with nutrition, cachexia is of early occurrence and is often extreme, but tumours of the breast and other regions protected from external contamination may attain quite massive proportions without giving rise to any constitutional disturbance.

In this connection it is interesting to note the observations of Bashford, Murray, and Cramer on tumour-bearing mice They found that mice might bear enormous tumours without showing any sign comparable to the cachexia seen in human beings, and this even when metastases had formed ; but ulceration of the surface of the tumour, with hæmorrhage and septic infection, resulted in emaciation and the rapid death of the animal.

There is no doubt that the symptoms of cachexia are often the result of the bacterial invasion resulting from superficial ulceration of a tumour, but the possibility of a chronic intoxication with its metabolic products, or the products of its necrobiosis, must not be lost sight of.

The blood changes in malignant disease are not characteristic. When present, they consist of an anæmia of the secondary or microcytic hypochromic type, varying greatly in severity. In carcinoma of the stomach, and of the alimentary tract generally, it may be profound, but for the most part the alterations appear to be the result of blood loss with or without secondary infection. In some cases of carcinoma of the stomach a macrocytic ("pernicious") type of anæmia is found, but this association is not as constant as theoretical considerations would suggest. Apart from the few cases of carcinoma which arise in a chronic gastric ulcer, achlorhydria is the rule in carcinoma. Hence a macrocytic type of anæmia might be predicted, but is not in fact always found. When present it responds to liver treatment. Leuco-erythroblastic anæmia may follow widespread osteoplastic secondary carcinomatous infiltration of bone.

(*h*) **Power of Continuous Growth.** Experimental studies have demonstrated that this is probably one of the most important attributes of malignant growths. Tumours which histologically show little or no deviation of structure from the parent tissues, and present none of the signs described above, are yet capable of unlimited propagation. While this fact is of the greatest importance in the theoretical consideration of malignancy, it is of little value from the standpoint of diagnosis in human cancer.

MULTIPLE TUMOURS

The simultaneous occurrence of two or more entirely different neoplasms in the same individual is so unusual as to excite attention, but it is a perfectly well recognised phenomenon, of which many instances have been put on record. The tumours may be innocent or malignant, of the same or different types, and situated in the same or different systems of the body.

The importance of the condition lies in the bearing it may have on the ætiology of tumours in general, and in the possibility of the different neoplasms having more than an accidental relation to one another. The upholders of the "cell-rest" theory of the origin of cancer have seen in this phenomenon support for their views, for where there is one congenital abnormality there may well be another. Others who postulate some constitutional disturbance, or a generalised lowering of resistance, as essential for the formation of a neoplasm, quote the concurrent growth of two tumours as evidence of such a change. Both claims, however, break down on examination.

Of much greater significance are observations in animals which show that, following the successful implantation of one malignant tumour in an individual, a second implant into the same animal may fail to develop. Some of the experimental tumours have no such effect and others may inhibit the development of an implant of a different type of tumour. The importance of these observations is obvious. They indicate clearly the presence of a profound constitutional change in the individual, brought about by the growth of the tumour, a very different thing from a hypothetical constitutional change which has been suggested as the cause of the development of tumours.

The demonstration of a sarcomatous transformation of the stroma which occurs in the course of the propagation of certain carcinomas of the mouse raises the question of the relationship of multiple tumours to each other. Many of these tumours in the human subject are, anatomically, widely separated, and can only influence one another indirectly But occasionally two tumours of different types occur in the same organ, and the possibility of the one providing the stimulus for the growth of the other immediately presents itself. So far, in spite of some suggestive observations, nothing definite can be said on this point.

It is scarcely necessary to insist that before a diagnosis of multiple tumours can be made, it is imperative that a thorough and critical microscopic examination be carried out, in order to make certain that absolutely distinct neoplasms really exist.

RETROGRADE CHANGES

Neoplasms are peculiarly liable to undergo forms of degeneration, and it is rare to find a tumour of any size which does not exhibit retrogressive changes to a greater or less degree.

These have been ascribed to the rapidity of growth of the tumour cells, to their imperfect powers of assimilation, and, in the case of metastases, to alterations in the food supply consequent upon a foreign environment.

The most important factors would seem to be the inadequacy of the vascular and lymphatic supplies. Owing to its rapid growth, the formation of the nutrient vessels of the tumour fails to keep pace with the development of the parenchyma cells, and it is only at the periphery that sufficient nourishment is obtainable. Similarly, the imperfect lymphatic system renders the renewal of the products of the cell metabolism an impossibility. Consequently we find the greatest changes occurring in the central parts of the more rapidly growing tumours, where a combination of insufficient nourishment and stagnation of metabolic products exists.

Fatty degeneration is one of the commonest forms to occur in tumours. It is associated with an imperfect blood supply and an anaplastic type of cell. It is therefore especially prone to appear in rapidly growing medullary or encephaloid cancers, though it may be seen in sarcomata and in innocent connective tissue and epithelial growths. It is a constant feature of hypernephromata, the cells of which are usually loaded with fat.

With ordinary methods of preparation, tumour cells often present a vacuolated appearance due to the solution, in the process of fixation and embedding, of the glycogen which they contained. This **glycogenic infiltration** can scarcely be deemed a retrogressive change, but is rather in the nature of a reserve food supply. It was formerly supposed to occur only in tumours derived from adrenal tissue, but further research has proved this view to be erroneous for it can be demonstrated in many different types of growth.

Mucoid "degeneration" is quite common both in epithelial and connective tissue tumours. When mucus can be demonstrated in the parenchyma of epithelial tumours there is no better reason for calling it a degeneration than for calling it a secretion It is commonest in tumours arising from mucous membranes that normally secrete mucus and so the question of degeneration should not arise. When, however, it appears in epithelium such as the breast which does not normally secrete it then the term degeneration may be justified. Both innocent

and malignant epithelial tumours may secrete mucus, but the carcinomata of the stomach, large bowel and gall bladder do so most frequently. The term " colloid cancer " for such tumours, though in general use, is, of course, a misnomer, for the product is a true mucin and has nothing to do with colloid as we know it in the thyroid gland.

Cystadenomata of the ovary frequently show what is known as mucoid degeneration, but in these tumours the substance formed is a *pseudomucin*, and does not give the chemical reactions of true mucin.

In connective tissue tumours the mucin is laid down in the matrix, and the cells of the growth are widely separated from one another. In this way are produced such mixed tumours as the myxofibromata and the myxochondromata. Among the malignant neoplasms of this class it is, as a rule, only in the slow-growing fibrosarcomata that myxomatous transformation takes place. Sarcomas may consist at least in part of myxomatous connective tissue.

Hyaline degeneration is seen in the stroma of slow-growing connective tissue tumours, especially the fibromyomata. It is also occasionally found in epithelial tumours, the individual cells of which become converted, entirely or in part, into masses of homogeneous hyaline material. These bodies may lie free among the cells of the tumour, or, if the cell concerned has not undergone disintegration, they may remain embedded in the cytoplasm, and they are of some importance since they have frequently been mistaken for forms of a cancer parasite.

Hæmorrhage into the substance of a tumour usually follows the rupture, either spontaneous, or the result of trauma, of one of its own vessels. It most often occurs in sarcomata, since in these tumours the vessels are ill-formed and supported by little more than the tumour cells, and are consequently unable to bear any considerable strain.

Necrosis may be quiet (necrobiotic) or inflammatory in nature. In the first case it results from insufficiency or obliteration of the blood supply to the part of the tumour concerned, and though the parenchyma is usually alone affected, large areas of parenchyma and stroma may necrose *en masse*. In encephaloid carcinomata, the central portions of the alveoli are often necrotic, while the peripheral cells, in closer relation to the nutrient vessels of the stroma, remain healthy and retain their staining reactions.

As the result of quiet necrosis large areas of a tumour may be converted into a cheesy material resembling the caseation of a tuberculous lesion ; or, again, the necrotic material may liquefy with the production of pseudocysts.

When invaded by bacteria, tumours, especially those on the surface

of the body, frequently undergo acute inflammatory necrosis with the production of offensive discharges and sloughing.

As has already been pointed out, the cachexia of cancer is largely due to necrosis of the tumour and the consequent absorption of the products of cell destruction.

Calcification, or **calcareous degeneration,** commonly follows extensive necrosis. It is irregular in its distribution, though it usually affects the centre or a thin peripheral zone of the tumour. Connective tissue growths, fibromas and myomas in particular, are peculiarly liable to it, and in a more limited degree it is not uncommon in epithelial growths. Small calcareous bodies are also a prominent feature in such tumours as the meningeiomata, and in these there is often a primary deposition of calcium salts without any previous necrosis.

Just as **ossification,** or true bone formation, may occur in calcified inflammatory foci, so it may appear in necrotic and calcified tumours. Nicholson[1] has studied the formation of bone in a benign calcified epithelioma of the skin, and has reviewed the literature on the subject.

In certain tumours, of which atrophic scirrhous carcinoma of the breast is the best example, there is an extensive production of fibrous tissue stroma. This **fibrosis** is not to be looked upon as a retrograde change in itself, but merely as an indication of the chronicity of the growth.

Amyloid disease, which is an extra-cellular deposit of a protein material often combined with chondroitin sulphuric acid, sometimes occurs in malignant disease. A few cases have also been reported in which tumorous masses of this material have appeared in multiple myelomatosis.

DISSEMINATION

Sooner or later every malignant tumour spreads beyond its site of origin and invades other tissues of the body, producing metastases, or secondary growths.

We have seen that in the course of its growth, a malignant neoplasm invades and destroys the tissues in its immediate neighbourhood; but, apart from this process of infiltration, we find secondary growths developing in parts of the body remote from the primary tumour, and separated from it by apparently healthy tissue. It is to such manifestations that the name **metastasis** belongs.

There is, of course, a superficial resemblance between this dissemination of a malignant growth and the extension of the inflammatory

[1] *J. Path. and Bact.*, 1918, **21**, 287.

process encountered in infectious conditions such as staphylococcal pyæmia, or tuberculosis. In both there occurs a primary focus of disease from which are derived secondary foci throughout the body; but it is scarcely necessary to point out that the formation of the secondary manifestations is entirely different in the two cases. In an infective condition, the infecting agent, staphylococcus, tubercle bacillus, or other organism, is transported to different organs of the body, where it causes a reaction of the tissues of the part and attracts wandering cells from the blood stream, the resulting focus being composed of a mixture of various elements. In malignant disease, on the other hand, the secondary nodule is formed by the lodgment and subsequent proliferation of tumour cells which have become separated from the parent growth, the fixed cells of the affected tissue and the wandering cells playing only a subsidiary part in the formation of the metastatic nodule.

Generally speaking, a malignant growth breeds true; that is to say, its secondary growths reproduce the features of the tumour from which they arose. But this rule is not absolute: often enough the histological characters of the primary and secondary growths show differences which are sometimes quite conspicuous. On the one hand, the metastasis may be apparently more benign in its character, growing expansively and compressing the surrounding structures rather than infiltrating them; or, on the other hand, the tumour may become more virulent as it disseminates, and the cells of the daughter nodules may assume a much more anaplastic type than those of the parent growth. So it frequently happens that the metastases of a spheroidal-celled carcinoma simplex of the mammæ assume an acinous type of formation, or scirrhous carcinoma of the breast gives rise to encephaloid metastases in the axillary glands and elsewhere Such variations are usually to be explained by a consideration of the structure of the organ in which the metastasis occurs. Loose, lymphadenoid tissue, for example, offers an extremely favourable nidus for the development of the malignant cells, and the study of small deposits in these and similar situations often throws a great deal of light on the nature of the primary tumour. In some instances, however, there seems to be no doubt that the virulence of the tumour cells increases with their dissemination.

Metastases exhibit an extraordinary degree of variation in size, number, time of appearance and clinical importance in the different classes of tumours, and in similar tumours of any particular organ.

Occasionally, the secondary growths may dominate the clinical picture, the primary tumour being insignificant both in its size and in

its local effect; indeed, the size of a malignant tumour bears no necessary relationship to the size or number of its metastases Thus, in an autopsy on a case in which the only possible clinical diagnosis was "malignant disease of the liver," that organ was enormously enlarged, weighing 119 oz., and was filled with metastatic growths which had destroyed the greater part of the gland (Fig. 3) Only after careful search was the primary tumour revealed in a small, flat carcinoma of the pelvic colon, ½ inch in diameter (Fig 4). There was some slight involvement of the mesentery opposite the affected portion of the bowel wall, but no deposits were found in any of the other organs.

Every pathologist could supply instances of such cases, but, as a

FIG. 3 Section of liver showing many large metastatic tumours secondary to the carcinoma of the colon illustrated in Fig. 4

rule, the primary tumour is larger than any one of its secondary growths.

In some cases, vast numbers of metastases are found at the post-mortem examination, involving almost every organ; many of them quite small, so that it seems as if an acute dissemination had taken place during the last weeks of life. In other cases, there may be no remote dissemination, the spread of the growth being entirely by a process of infiltration.

The position in which secondary foci develop is a point of very considerable interest. The metastases of various tumours show a remarkable tendency to appear in certain tissues or organs, while other situations seem to be almost immune to secondary deposits from any form of growth. We know from experience that in all forms of

carcinoma involvement of the neighbouring lymphatic glands is usually present; growths of the alimentary canal often give rise to metastases in the liver, and the bones are commonly affected in tumours of the thyroid and prostate glands. Other organs, such as the kidney, pancreas, and brain, are less frequently involved, and only in extreme dissemination are metastases found in the spleen, the intestines, and the skeletal muscles.

Though such peculiarities may often be explained by anatomical or

FIG. 4 Pelvic colon opened to show a small flat carcinoma (A) which gave rise to large secondary deposits in the liver (Fig. 3).

mechanical considerations, we are faced by the fact that certain tissues appear to offer an unusually favourable nidus for the metastases of particular tumours; they are, in fact, tissues of predilection.

Sampson Handley, in his exhaustive study of dissemination in cancer of the breast [1] has demonstrated that the bony deposits so often met with in this condition are but a part of the general permeation of the body which extends, in ever-widening circles, from the primary growth. But such a process will not explain the extraordinary number of metastases found in the bones in cancer of the prostate, where deposits in the soft parts may be limited to the lumbar lymphatic glands, whilst

[1] *Cancer of the Breast*, London, 2nd edition, 1922.

the bones, including those of the skull, may be riddled by them. Again, the liver, receiving the blood from the portal system, is likely to be affected in tumours of the intestine ; but this is no reason why it should be so commonly involved, as it is, in melanomata of the skin and the eye

A question of great importance is that of the period of the disease at which secondary manifestations appear. Some tumours disseminate with appalling rapidity, so that within a few weeks of the recognition of their presence such extensive metastases occur as to render surgical interference quite hopeless. In other cases, dissemination is slow and limited in extent, and complete removal of the affected organ with the secondarily affected area may result in cure. But in such circumstances a considerable interval of time must elapse before a cure can be claimed, and for this reason : metastases may remain latent in the tissues for long periods though still retaining their vitality. Cases have been recorded in which twenty, or even thirty, years elapsed after the removal of the primary tumour before secondary manifestations appeared. These cases are, of course, exceptional, but it is quite *common for secondary growths to appear two or three years after the* removal of the original tumour. No theory is adequate to explain how the seeds of such metastases can remain latent for so long a period, retaining their vitality and maintaining their footing in an unusual situation, or why they should suddenly assume an excessive proliferative power ; but the fact remains, that no case of cancer can be considered to have been cured by an operation until at least three years have elapsed without signs of recurrence, and even then the prognosis is little more than favourable. It may be that local recurrence is not always metastatic, but sometimes of the nature of an entirely fresh growth ; the influence which gave rise to malignant change in the cells of an organ may still be potent to affect any remains of that organ which may have been left undisturbed at the time of operation. For instance, an undoubted malignant papilloma may be found on the dorsum of a tongue, part of which had been removed for cancer fourteen or more years before. The growth may have all the appearances of being primary and the possibility of its being secondary would appear to be negligible.

An operation for the cure of cancer can only be successful when the whole growth is removed ; *if a single metastasis is overlooked*, the proceedings are doomed to failure. So, if surgical measures are to be of any value, it follows that the spread of the growth must be of limited extent. Further, it is essential that the operator should be acquainted

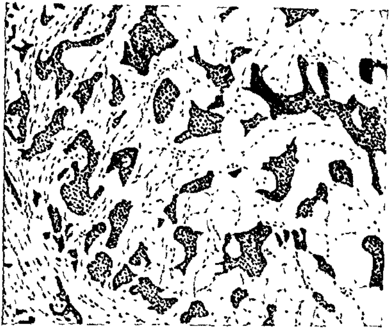

FIG 5. Section from the growing margin of a carcinoma simplex of the breast Groups of carcinoma cells infiltrating fatty tissue.
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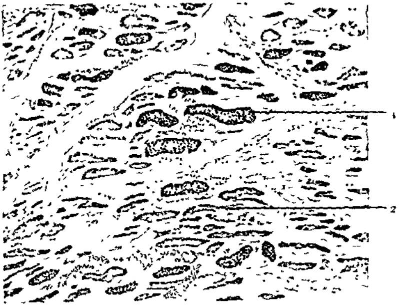

FIG 6 From a carcinoma simplex of the breast Groups of malignant cells (1) infiltrating between muscle fibres (2)
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with the modes or paths of malignant dissemination if he is to plan his excisions so as to include zones of probable infiltration

The process of local infiltration is well understood. It consists

essentially of an extension of the growth in lymphatic spaces and along fascial planes; in fact, extension along the lines of least resistance (Figs. 5 and 6). But the explanation of the formation of remote metastases is more difficult, and is complicated by the fact that, as a centre of dissemination, every secondary deposit may behave as a primary growth. In this way the paths of infection in any particular case are often obscured; and the obscurity may be deepened by the simultaneous occurrence of two or more processes of extension.

For practical purposes three methods of dissemination may be distinguished.

1. Transplantation.
2. Permeation.
3. Embolism.

1. Transplantation

Several varieties of dissemination may be distinguished under this heading; they include all those forms which essentially take place without the aid of lymph or blood vessels.

(*a*) **Transplantation by Apposition.** This method is by no means of frequent occurrence. It consists in the infection of a surface by actual contact with a malignant growth, and there must almost certainly be some abrasion of the infected surface for the successful lodgment of the malignant cells to take place. Instances which may be encountered are the transference of growth from a carcinoma of the lip to the other lip, and of carcinoma of the cervix uteri to the wall of the vagina. Cells from an extensive carcinoma of the breast may become grafted on to the patient's arm should that limb be fixed to the affected side from one cause or another and instances have been recorded in which such transference has taken place into the incisions made for the insertion of silk drains in a case of brawny œdema of the arm. Under the heading transplantation by apposition, we may include those cases of dissemination in a hollow viscus, the most obvious example being found in the villous papilloma of the urinary bladder. Here, contact between the tumour and the bladder wall results in the formation of a secondary tumour, and so the condition spreads until a considerable number of tumours are present on the wall of the viscus.

In this division may be grouped those rare instances of transplantation occurring in the alimentary canal, where a nodule of growth may become attached to, and grow in, the wall of the canal below the primary tumour. In these cases it is difficult or impossible absolutely to exclude dissemination by embolism or permeation, or even the occur-

rence of multiple primary tumours, and it is by no means easy to understand how successful transplantation can take place.

(*b*) **Transplantation in Serous Cavities.** Should a malignant growth burst through the lining membrane into a serous cavity such as the peritoneum or the pleura, it is easy to understand how small groups of cells, separated from its surface, may be planted on to the membrane in the immediate neighbourhood of the tumour, or transported to distant parts of the cavity by the movements of the contained viscera. Having once obtained a footing, they will proliferate and give rise to definite metastases (Fig. 7). Such a mode of spread is well seen in ovarian tumours and certain growths of the stomach, especially the

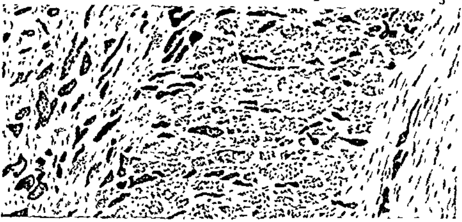

FIG 7 Carcinomatous dissemination in the peritoneal cavity Section of vermiform appendix showing malignant invasion of the wall from without inwards—secondary to carcinoma of stomach (1) Serous coat, (2) outer muscular coat (3) inner muscular coat

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"colloid" carcinoma. Sampson Handley would lay great stress upon this process in the spread of carcinoma of the breast when the malignant cells permeate the chest wall and enter the peritoneum at the epigastric angle This process may be, and commonly is, associated with permeation of the subserous lymphatics, and in cases of advanced malignant invasion of the peritoneum or the pleura many of the nodules of growth are outcrops from the permeated lymphatics, and are not true examples of transplantation.

(c) **Inoculation.** The experimental study of cancer has demonstrated the ease with which auto-inoculation, the inoculation of a tumour-bearing animal with particles of its own tumour, may be performed. So it is not surprising to find a similar process occurring in malignant disease in the human being. If, in the course of its removal, a malignant growth be opened, there is a grave risk of escape of groups of the

tumour cells into the exposed tissues of the wound, the probable result being an early local recurrence ; and it is quite certain that a scalpel or needle, contaminated by contact with the growth, may be the means of conveying the infection. Sir Bernard Spilsbury kindly allows us to quote the following case in illustration of this process. An abscess of the liver was suspected in a patient who presented an anomalous enlargement of that organ, and the tumour was explored with syringe

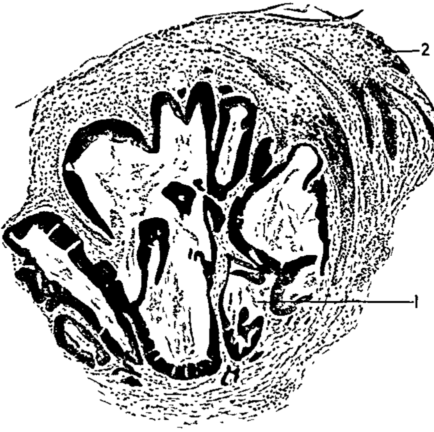

FIG 8 Inoculation of carcinoma into the skin of anterior abdominal wall (1) Columnar celled carcinoma ; (2) superficial epithelium
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and needle by the house physician No fluid was withdrawn, but in the bore of the needle Spilsbury detected a small shred of tissue ; he was able to prepare sections of this, and found it to be a fragment from an adenocarcinoma. The patient was discharged, but returned to the hospital some time afterwards, coming under the care of the same house physician, who noticed a small nodule in the skin of the anterior abdominal wall at the site of the previous exploratory puncture. This nodule was excised, and examined by Spilsbury ; it was a nodule of

adenocarcinoma (Fig. 8). Later, the patient died, and at autopsy a primary adenocarcinoma of the liver was revealed.

2. Permeation

The recognition of this mode of spread is due to the researches of Sampson Handley. As the result of his extensive investigations into the spread of cancer of the breast, he came to the conclusion that the vast majority of metastases are due to a process which he termed lymphatic permeation. By this term is meant the gradual extension of the outlying processes of the tumour, in the form of solid plugs or columns, into and along the large lymph vessels (Fig. 9). As the result

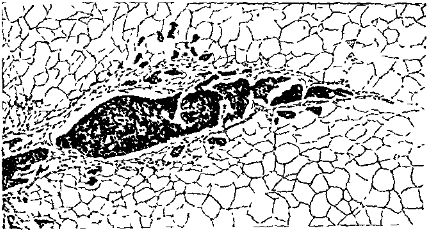

Fig. 9. Section from periphery of a carcinoma simplex of the breast showing permeation of a lymphatic vessel by carcinoma cells
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of the distension of the vessel thus produced, the wall becomes stretched and eventually bursts , but before the stage of rupture is reached a peri-lymphatic reaction or inflammation, consisting in a proliferation of fibroblasts and an accumulation of round cells, is usually evident, and becoming more intense ends in the choking and killing of the cancer cells. Extension of growth, however, proceeds at the distal end of the plug, and so it comes about that a solitary nodule may develop at some distance from, and apparently unconnected with, the primary tumour Sampson Handley does not deny that embolism may play a part in the dissemination of malignant growths of the breast, but he believes that permeation is the major process. Further, this investigator has shown that permeation occurs by choice in lymphatics of not less than 40–50μ diameter, avoiding the smaller vessels and the larger trunks where the force of the stream is sufficient to sweep the cells away as emboli. Later

histological research has failed to confirm the frequency of carcinomatous permeation followed by fibrosis, but has amply confirmed both embolism and permeation. Superficially, the process of permeation thus described closely resembles the infiltration which is such a distinctive feature of malignant tumours ; but, as Handley points out, the two are distinct and differ in important particulars.

Infiltration takes place in tissue interspaces, is the earliest disseminative process, and is best seen at the macroscopic growing edge ; permeation occurs later, is limited to lymphatic vessels as opposed to

FIG. 10. Section of a carcinoma of the breast showing permeation of a duct. (1) Carcinoma ; (2) duct epithelium.
Obj. 8 mm apochrom. Comp. oc. 4. Tube length 160 mm.

lymph spaces, and is best seen in the microscopic edge of growth often 6 inches from the apparent margin of the tumour.

Infiltration is a slow process, since the tissue spaces are small and often interrupted ; permeation is comparatively rapid, the larger channel offering less resistance to the advancing column, and is therefore by far the more important.

The two processes are, of course, interchangeable. Infiltration will occur round the secondary nodules resulting from permeation, and infiltrating cells will spread by permeation should they chance to invade a lymphatic vessel. It becomes obvious, therefore, that the study of the anatomy of the main and subsidiary lymphatic systems of the body is of the highest importance to the operating surgeon, for only by

recognising the probable paths along which permeation will take place can he plan his operations with any hope of success.

Although permeation occurs chiefly along lymphatics, it must not be forgotten that it may take place along veins or ducts (Fig. 10). The most frequent examples of macroscopic venous permeation are seen in Grawitz carcinoma of the kidney, and the most famous example is the malignant testicular chondroma of Paget, afterwards described as a carcinoma by Kanthack and Pigg [1] and a teratoma by Nicholson,[2] where the growth permeated the spermatic vein, eventually entering the vena cava. An interesting form of permeation is that occuring in the lymphatics of nerve trunks. There is some evidence to show that

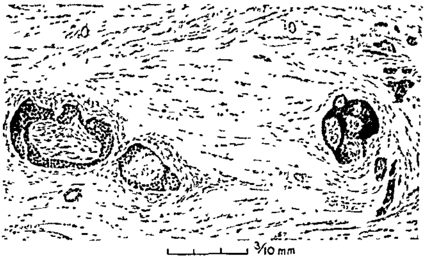


FIG. 11 Nerve invasion in carcinoma of the uterus Section of the parametrium showing permeation of the perineural lymphatics by columns of carcinoma cells

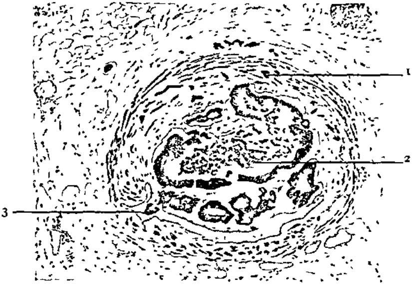
this form of dissemination may be of considerable clinical importance (Fig. 11).

3. Embolism

The majority of metastases are produced by the carriage of individual cells or small groups of cells by lymphatics, blood or other channels. Carcinomata generally metastasise first to lymphatic glands and later by the blood stream to other parts of the body. Sarcomata metastasise to lymphatic glands, but because of the early blood spread from these tumours the lymphatic spread is often inconspicuous. The only possible explanation of the majority of visceral metastases is that cells have been conveyed to the new site by the blood stream. The order of frequency in the appearances of metastases confirms this view.

[1] *Trans. Path Soc Lond*, 1897, **48**, 150.
[2] *Guy's Hospital Reports*, 1907, **61**, 249

Secondaries appear most frequently in the lungs in most carcinomas except those which arise in organs with a venous supply which drains to the portal system and in these the metastases appear first in the liver. Apart from lymphatic glands the order of frequency in general is *lung, liver, brain, bones. There is no priority among the remaining* organs There are some carcinomata which show peculiar selection in the sites in which their metastases appear. For instance, carcinoma of the bronchus very frequently produces secondaries in the adrenals and almost as often in the brain. These tumours often produce very



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widespread metastases, almost all the organs and tissues of the body being affected. Another example of peculiar selection is the well-known association between carcinoma of the prostate and widespread bony metastases. Grawitz carcinoma of the kidney early infiltrates the renal vein and may at any time produce widespread metastases. As has been mentioned before the primary growth may give rise to no recognisable signs or symptoms while one or other of the secondaries may be the cause of all the signs and symptoms from which the patient suffers. Of these silent primaries the bronchus, kidney and prostate are the most important. Although emboli from carcinomata are very common it does not follow that single cells or small groups of cells will inevitably produce metastases. It is certain that many emboli pass into organs

all over the body and only a few of these grow, the others being destroyed.

Retrograde Embolus. In lymphatic glands the metastases appear first in those glands to which the lymph flows from the site of the primary tumour. When, however, the channels to a group of glands have been blocked by growth, metastases may appear in glands to which the lymph does not normally drain. This is called **retrograde spread** and may occur by the carriage of emboli if the flow of lymph has been reversed or by the permeation of the channel by a thread of growth.

ÆTIOLOGY

Probably no disease has excited more general speculation as to its cause than cancer. This speculation is just as rife amongst the lay public as it is amongst doctors, and the views advanced are often more coloured by crank or phobia than by the least trace of scientific evidence.

When we speak of the cause of cancer we make two assumptions, neither of which is necessarily justifiable; we tacitly assume the essential similarity of all the proliferative lesions which exhibit autonomous, continuous and invasive growth; and we take it for granted that all these tumours are the result of the action of a single cause. The first of these assumptions is more likely to be true than the *second, but neither is immune from criticism*; and while it is generally assumed as a basis for investigation, that all tumours are alike in their *fundamental characters and their ætiology*, it is possible that in thus simplifying our problem, we are actually complicating it.

A clear-cut difference should be made between (*a*) the remote, and (*b*) the intrinsic causes of cancer There is no serious difference of opinion about the remote causes; they are the chemical, physical, hormonal and other agents that excite cell proliferation which may end in the production of a tumour. The intrinsic cause is the one which is responsible for the change in the individual cancer cell which results in its continued tumorous behaviour no matter how far removed it may be from the remote cause. In X-ray cancer the cells continue to multiply long after the remote cause—the X-rays—have ceased to operate. It must be frankly admitted that while we do know a v[illegible] great deal about the remote or extrinsic [illegible] we have no knowledge of the intrinsic cause.

Before discussing the various theories [illegible] been adva[illegible] from time to time to explain the occurren[illegible] it would

well to consider those more general conditions which might be expected to exercise influences of varying degree of importance.

It must be recognised that the available statistics bearing on these conditions are far from satisfactory. The records of the Registrar-General are imperfect, since the majority of the diagnoses rest upon clinical evidence alone ; and, while hospital figures are more reliable, they are not free from error and because they refer to a somewhat restricted class of the community often give misleading figures.

However, as the result of careful investigation, certain facts may be regarded as having been definitely established.

Incidence. In England and Wales about 70,000 persons die every year from cancer out of a total death rate of 480,000 and a population of 41,500,000. Almost half the total cancer mortality occurs in persons of sixty-five years or over and as the longevity of the population in this country has been steadily rising, there is an apparent increase in the incidence of cancer. If the figures are corrected by calculating the cancer mortality rate for a standard population of persons divided into age groups, a more accurate impression is gained and it is at once clear that the increase is not so great. For instance, the crude death rate for cancer at all ages in 1935 was 104 per cent. higher for males and 55 per cent. higher for females than in 1901–10, but if standardised rates are compared, these figures are reduced to 35 per cent. and 2 per cent respectively.

Comparative figures from those countries in which statistics are available show that although the incidence of cancer is approximately the same, yet the organ of incidence varies in different countries and between the sexes. Cramer [1] has emphasised this point and suggested that although the development of malignancy in a given site is a strictly localised process, it is dependent on factors outside the site. These may be regarded as general or systemic factors and this suggestion is supported by experimental work.

Origins. As far as the human body is concerned tumours may arise in any of the cells of its tissues or organs. There are no cells that are exempt from this liability. Tumours are also universally distributed throughout the animal kingdom.

Age. Some classes of tumours show a definite age distribution, but variations frequently occur and it is only possible to make a few broad generalisations under this heading. With the exceptions of a few congenital neoplasms, certain sarcomata and such innocent connective tissue growths as the chondromata, it may be said that tumour

[1] *Lancet*, 1934, i, 1.

formation is rare before adolescence. After this period there is, with increasing age, an increasing liability to both the innocent and malignant form of tumour

It was formerly believed that sarcomata appeared mainly in young adults, but this is not true, for recent figures show that the age incidence of this class of tumour resembles that of the carcinomata, increasing up to the age of fifty-five and then diminishing by degrees. Sarcomata, however, certainly differ from carcinomata in that a far greater proportion occur before the age of twenty-five.

Sex. *There is very little difference between the sexes in the incidence* of cancer. In 1940 the actual deaths from malignant disease in England and Wales numbered 33,135 among males and 35,605 among females; this corresponds to standardised mortality rate per million of 1,063 males and 920 females Until about 1923 the official figures suggested that cancer was more frequent in women than in men.

Organ Distribution. Although there is so slight a difference between the actual figures in the two sexes, the incidence of cancer in the different organs varies considerably as is shown in the table on opposite page.

It will be seen that the breast and uterus are the seat of one-third of all cancers in the female, whereas the corresponding organs in the male only constitute 7 per cent. of the total. This emphasises the liability to malignant disease of organs which throughout life are the seat of active cellular and vascular changes. For example, cancer is exceedingly rare in the male breast and in man that organ is rudimentary and functionless; in the female, on the other hand, this form of tumour provides one-fifth of the fatal cases and the gland is active, actually or potentially throughout a long period and is subject to important involutionary processes.

In males there is a higher incidence of cancer in those sites particularly exposed to external influences These figures also give some indication of the changing incidence of cancer in different organs. For example, in males there has been a slight but steady increase in gastro-intestinal cancer, although the tongue and lip has decreased and there has been an apparent increase in prostatic carcinoma. In the female there has been a greater decrease in uterine cancer, but a steady increase in that of the breast. In both sexes the incidence of pulmonary cancer has shown an increase, particularly in the male. Although these changes are of interest, it is dangerous to pay too much attention to them; increased skill in and opportunities for diagnosis and changes in medical fashions all play their part in modifying statistics.

Standardised Death-rates per Million for Cancer of Different Sites (by pre-1940 Classification in 1911–20, 1921–30, 1931–35 and by 1940 Classification in 1931–35 and 1936–40)

	Pre-1940 Classification			1940 Classification	
	1911–20	1921–30	1931–35	1931–35	1936–40
Males					
All sites	897	1000	1045	1021	1045
Tongue	50·8	45·9	36·7	35·0	27·6
Œsophagus	60·6	64·1	60·3	59·1	51·2
Stomach	186·4	220·2	232·1	228·6	230·7
Intestine	96·8	124·8	137·6	131·6	137·4
Rectum	93·6	105·0	111·6	107·7	108·9
Testes	4·9	5·8	6·4	6·2	7·0
Prostate	26·5	47·3	58·2	55·9	61·2
Penis and scrotum	9·0	9·1	8·6	7·8	6·9
Breast	1·6	1·8	2·1	2·0	2·0
Lung	12·7	25·1	66·7	66·4	109·2
Bladder	28·2	30·3	33·0	32·0	33·2
Skin	24·3	26·9	23·5	21·1	19·8
Females					
All sites	959	980	969	942	927
Tongue	4·3	3·8	3·5	3·4	3·5
Œsophagus	16·5	18·0	19·1	18·7	18·3
Stomach	139·9	154·2	155·2	152·1	146·5
Intestine	109·2	128·5	138·2	132·8	133·6
Rectum	59·3	59·3	58·2	56·2	55·4
Ovary	24·3	36·1	45·4	44·8	51·0
Uterus	174·4	157·7	136·3	132·4	123·0
Breast	170·8	188·4	197·7	187·5	187·0
Lung	7·0	9·6	18·8	18·8	25·7
Bladder	9·7	11·3	11·1	10·9	11·6
Skin	15·2	14·9	13·5	12·4	11·4

These figures were kindly supplied by the Registrar-General's Office.

Heredity. While in man there is no definite evidence of inheritance of tumours themselves there is evidence of inheritance of abnormalities which are commonly associated with the development of tumours. Polyposis coli, for instance, is a familial disease, and if patients having this condition survive long enough carcinoma of colon will almost certainly develop.

Only in recent times have attempts been made to study cancerous inheritance in man on an adequate scale. The most extensive and determined have been made by Waaler in Norway and Wassink in Holland. These investigators had adequate material, 6,000 and 2,472 cases respectively, and inquired into the near and more distant family histories. In general it may be said that their reports suggest

that hereditary predisposition may be organ specific and sex conditioned, particularly in the female. Patients having carcinoma of breast or of uterus had a greater proportion of female relatives having a like carcinoma than would be expected in women in general. They failed to find any hereditary influence in cancers which may be related to extraneous factors, such as cancer of lip. In spite of the very great difficulties due to "chance" mating in man and to unreliable records of cause of death and failure to trace relatives, it appears that there may well be familial tendencies to the development of abnormal proliferations in particular organs. But there is no conclusive evidence in man that the actual tumours are inherited. This view has been strikingly vindicated in recent times in animal experiments. Murray found that cancer developed in the breast of mice far more frequently if their mothers or grandmothers had had cancer of the breast. Since that time, by selective inbreeding, strains of mice have been developed in which, if they live long enough, 75 to 90 per cent. of the females will develop carcinoma of the breast. It seemed to be quite clear from a mass of work of a number of investigators in different countries that in mice there was a hereditary carcinomatous factor which could be developed by inbreeding and which was specific for a particular organ. Other lines of mice have been bred in which there is little or no spontaneous development of breast carcinoma. Some investigators believed that they had proved that susceptibility and insusceptibility behaved as Mendelian recessives or dominants. In fact it is now clear that susceptibility and insusceptibility to carcinoma of the breast in mice depends on a number of factors. The simple genetic theory of susceptibility was first questioned when Loeb as long ago as 1916 showed that the surgical removal of the ovaries of young mice of a high cancer strain reduced the incidence of carcinoma.

This suggested that an internal secretion of the ovary played some part in the actual development of carcinoma of the breast in susceptible mice. The suggestion was confirmed by Lacassagne who found that following the administration of œstrone to male mice of a high cancer strain carcinoma developed, whereas without œstrone the males did not develop cancer. It was further shown that in low cancer strains, neither male nor female mice showed an increased incidence following administration of œstrone. There appears to be a quantitative relation between the hereditary tendency and the œstrogenic substances. If the hereditary tendency is strong, carcinoma will result from a minimal œstrogenic stimulus, if it is weak it will require maximal stimulation to produce carcinoma.

The hereditary principal appeared to be sex linked. In hybrids resulting from a cross between a high cancer strain mother and a low cancer strain father, the offspring showed a cancer incidence similar to that of the mother. In hybrids resulting from a cross between a low cancer strain mother and a high cancer strain father the offspring also showed a cancer incidence similar to the mother.

A further and startling complication arose when it was shown by Bittner that if newly born mice of a high cancer strain are removed from their mothers and fostered by mice of a low cancer strain the incidence of carcinoma falls significantly. It has now been shown that when a high cancer strain is bred and the young fostered so that they are deprived of their own mother's milk, the cancer incidence remains low. All the hereditary factors are, however, preserved and the high cancer incidence can be restored by feeding with milk from a mother of a high cancer strain. Three factors appear to play a part in the production of spontaneous mammary cancer in mice: (1) a hereditary factor, (2) the ovarian factor, (3) the milk factor. The first and second are internal and the third an external factor. The nature of the hereditary factor is unknown. It may be hypersensitivity of the epithelial cells of the breast so that they respond by atypical overgrowth to a normal ovarian stimulus. Without the extraneous factor, in this case the milk factor, carcinoma does not develop.

The milk factor appears to be universally distributed in the animal as it has been recovered from the blood the spleen and the thymus. It has many of the features of a virus; it is particulate, can be dried and passes a fine filter

In-breeding of the kind necessary to produce these pure cancer-prone or cancer-resistant mice has no counterpart in man. And since it has now been shown that the inherited factor under these controlled conditions is not enough of itself to produce cancer, it is unlikely that it has a more dominating influence in man.

Locality.[1] Analysis of the statistics of cancer incidence in different parts of countries or even of towns shows wide variation, both for the total number of cases and for the site affected. For most cancer sites the death rates for a given age are higher for the urban than for the rural areas. There are in addition large geographical differences in the incidence of cancer of the various organs. There are also social differences. The mean death rates in 1930–32 show that at each age group the rate for uterine cancer was lower amongst single than other women and increased amongst married women on descending the social

[1] Stocks, P., *Brit. Emp. Cancer Camp. An. Report*, 1939, 308.

scale, whereas breast cancer showed the exact opposite. Neither the social nor the industrial variations account for the geographical differences either of the total incidence or the site incidence.

Civilisation. From time to time one hears it asserted by those who lean towards the simpler life that cancer is a disease of civilisation. Exactly what is meant by this is difficult to say. If by civilisation is meant the direct opposite of barbarism or "wildness," the phrase is meaningless, for there can be no possibility of comparing the cancer incidence in civilised and uncivilised communities. The ultimate diagnosis of cancer rests on a histological basis, its presumptive diagnosis on skilful clinical and post-mortem examinations. The uncivilised are usually outside the scope of these procedures, and even if by chance the presence or absence of malignant disease can be established in any particular barbarian, this means nothing in the absence of numerical data of the total population and age distribution of large numbers of barbarians, together with controlled statistics of the causes of death among them. The same applies to animals. We know that cancer occurs in domestic animals, and statistics are available of its incidence in animals bred in captivity, but it is impossible to say what proportion, if any, of the total population of, say, lions, dies from cancer. If, on the other hand, by civilisation is meant the mode of life peculiar to particular communities of individuals, then it may be pointed out that there exist at present many civilisations, and there have existed in the past very many more, all differing profoundly from one another. While, therefore, there is no general factor which we can call civilisation, there are factors in different civilisations which undoubtedly predispose to cancer. The simple native of Kashmir, for example, does not suffer from mule-spinner's cancer, but then neither does the cotton operative of Lancashire develop cancer of the anterior abdominal wall, for the Kangri does not enter into his scheme of life. Two alleged concomitants of civilisation—auto-intoxication due to intestinal stasis, and improper dietary—have been particularly blamed of recent years for the supposed increase of malignant disease among our population, but it is difficult to see with what justification. A glance through the pages of Pepys' diary reveals the fact that constipation was as common 300 years ago as it is to-day, and unless the vast sums of money spent every year in advertising aperient and purgative medicines are entirely wasted, it would seem just as logical to argue that cancer is due to intestinal unrest, for it is difficult to imagine the modern civilised intestine remaining static for any length of time.

As far as one can see, the influence of food as such in the development

of cancer is negligible, though the temperature at which it is served and the condiments and artificial stimulants which sometimes accompany it may possibly not be without effect. Cancer occurs in races of mankind and in animals differing so widely from one another in their diet that any food factor common to them all can hardly have escaped notice. There is certainly no evidence that either an excess or a deficiency of vitamins has any action on the growth of the transplanted neoplasm in animals; and though it has been suggested that a deficiency of, especially, vitamin A may be followed by epithelial hyperplasia, such reactions are not recognised as proceeding to malignancy.

A study of the incidence of cancer of the penis gives some indication of the influence which custom may have on the incidence of the disease in particular organs. Cases of cancer of the penis in uncircumcised Jews have been recorded, but there is no recorded case of cancer of the penis arising in a circumcised Jew. Although the incidence is very small, cases have been recorded among Moslems. Wolbarst [1] suggests that the difference between Jews and Moslems might be due to the differences in the customs of these two peoples. The Jews circumcise on the eighth day of life, the Moslems between the fourth and ninth years.

Precancerous Conditions. In man there are many conditions which we know by experience are associated with the development of a carcinoma. To what extent are we justified in regarding these conditions as precancerous? Experimental tar carcinoma shows a sequence of changes in the skin before development of the actual carcinoma Similar changes precede carcinoma in the workers in industries using tar and tar products. Chronic inflammatory infiltration, papillomata and finally carcinoma are the steps in the development of these growths. These facts add cogency to the inquiry into the relation between chronic inflammation, atypical cellular proliferation, benign tumours and cancers. Many carcinomas such as those arising in tongue and lip, or cervix uteri are often preceded by chronic inflammatory reaction. Others arise in glandular organs in which there is already atypical cellular proliferation. Primary carcinoma of the liver is a good example of this kind. It is not a common tumour, but when it does occur it is commonest in fibrotic livers and in these it arises from regeneration nodules. Atypical hyperplasia of the breast as seen in the adenomatous hyperplasia (chronic mastitis) is often found in the same breast as carcinoma Chorion carcinoma most commonly follows a hydatidiform mole. Benign tumours sometimes change their nature

[1] *Lancet*, 1932, i 150

and become malignant. The familial condition polyposis of the colon shows a clear-cut association between benign and malignant adenomatous polyps. Can it be assumed that the natural history of all these conditions is towards tumour formation and malignancy? At present all that is known about tumour development suggests that it is not; but when a tumour is to develop it is likely to do so in cells that are already in an active stage of proliferation. It follows that chronic inflammation, atypical hyperplasia and benign tumours are the soil in which tumours may develop and not that they are essentially a stage in the development of cancer.

Trauma. Mechanical trauma is commonly thought by patients to be intimately connected with the development of their particular tumour. And sometimes this belief leads to claims for compensation. Ewing, in a detailed examination of the predisposing effects of trauma, points out: (i) that the incidence of well-attested traumatic tumours is extremely low (ii) experiments in the production of tumours indicate that trauma is incapable of producing a malignant tumour in normal tissues, and (iii) "The clinical impression that normal tissues may react to injury by malignant proliferation is so much at variance with what is known about the origin of most tumours that it has always been regarded with scepticism." He admits the rare cases of "acute traumatic sarcoma in which there is almost unbroken continuity of symptoms of injury and malignant tumour." On the whole the evidence suggests that in all except the rarest of cases the injury calls attention to a previously unnoticed tumour and is not the cause of it.

Experimental evidence adds a little to the complexity of the relationship of trauma and tumour. Peyton Rous has shown that cells which have already become malignant may be dormant and indistinguishable from a normal cell in appearance and function for a long time. Thus tar painting of rabbit skin will after a short time bring about irreversible cancerous change in cells of the epidermis, but cancer will not develop except by further tarring or application of some other irritant. Some twenty years ago Deelman found that the repair of wounds in the tarred skin of mice was often accompanied by the development of either papillomas or carcinoma at the edge of the wound. These observations have recently been confirmed by Pullinger; it is possible, therefore, that in man trauma may sometimes be the immediate non-specific cause for the development of a tumour in cells that have already become tumorous.

Occupational Cancer. Pott, in 1775, drew attention to the excessive

incidence of scrotal carcinoma in chimney sweeps. A similar association has been found in workers with tar and its derivatives, in X-ray and radium workers, in the Schneeberg miners, aniline dye workers and following Kangri burn among natives of Kashmir. One of the important facts which a study of these tumours has demonstrated is that there is a latent period of from ten to fifteen years or more between the exposure to the exciting cause and the development of the tumour.

These occupational cancers provide the closest resemblance in man to an experimental study of this disease and much has been learnt of their causation and some of the factors which play a part in cancer production. Thus a large number of workers may be exposed under roughly similar conditions, but only certain of them will develop cancer. This has been explained on the basis of the varying susceptibility of the individual to the stimulus ; the underlying factors of this susceptibility or immunity are not known, but heredity may play some part.

After some years tar workers may show localised thickening of the skin, pigmentation and areas of hyperæmia and then papillomata appear ; after a further interval, a carcinoma may develop in one of these sites. In many cases, the malignant growth does not appear until after the worker has ceased to be exposed to the exciting cause. An interesting sidelight on this latent period is shown in Pott's original account of the chimney sweeps' cancer in which he mentions that the common onset of the disease is between the ages of thirty and forty, and since the sweeping of chimneys was commonly performed by children, this corresponds to the latent period found to-day.

Adequate screening has eliminated the risk run by radiologists and adequate protection of the skin, increased cleanliness and the change to a non-carcinogenic lubricant have greatly reduced the incidence of occupational cancers.

OCCUPATIONAL CANCER

Human	Experimental
Physical Agencies	
1 *Heat*	
Carcinoma on the shins of engine drivers (Murray, 1920)	No counterpart.
Carcinoma of Kangri wearers of Kashmir (E Neve, 1910).	
(In both these examples there is the possibility that the cancers arise in the scars of burns or as a result of exposure to coal tar products)	

OCCUPATIONAL CANCER

Human	Experimental
Physical Agencies	
2. *Solar radiation* (Unna, 1894). Carcinoma on the exposed parts of mariners, agricultural workers, etc High incidence of rodent ulcer among the fairskinned persons in Australia	Findlay produced epitheliomata in mice after 8 months' exposure to ultraviolet light. Roffo produced carcinomata and sarcomata in rats after 11 months' exposure to sunlight.
3. *X-radiations* (Frieben, 1902). Carcinoma and sarcoma in radiologists working without proper protection (incubation period 4–9 years). Carcinoma following X-ray treatment for lupus.	Sarcomata in rats and epitheliomata in rats and mice after a year's repeated radiation.
4. *Radioactive substances.* Lung cancer in radium laboratory worker (Neitzel, 1935). Bone sarcomata in luminous paint workers after 7 years (Martland, 1929). *Malignant hæmangeioma of the* liver 3 years after a radium needle had become accidentally implanted in the vicinity (Ross, 1932). *Lung cancer in Schneeberg and* [illegible] Hesse, 1879).	Sarcomata and carcinomata produced in animals with screened and unscreened radium in 6–18 months. Sarcomata produced in rats and mice with thorotrast in 9–18 months.
Chemical Substances	
1. *Soot* (Percival Pott, 1775). Cancer of scrotum in chimney sweeps.	Ethereal extracts or extracts in human serum have produced the condition in animals
2. *Tar and kindred substances.* Tar and pitch (Volkmann, 1875). Carcinoma of hands and scrotum in workmen engaged in making patent fuel, tar distillation, gas works, carbon electrode makers.	Identical substances have produced carcinomata and sarcomata in mice, rats and rabbits Incubation period in mice 4 months.
3. *Paraffins* (Joseph Bell, 1876). Carcinoma in shale oil refiners. Incubation period 20–30 years.	Reproduced in mice.
4. *Lubricating oil* (Dr. Wilson, 1910). Carcinoma of scrotum in cotton spinners. Incubation period 10–30 years.	*Reproduced in mice.*
5. *Aniline* (Rehn, 1895). Carcinoma of the bladder in aniline dye workers. Incubation period 20 years.	Reproduced in dogs after the ingestion of beta naphthylamine

tions of animals of the same species; but the meaning of these observations escaped notice, and it was not until Jensen reported that he had been able to propagate a mammary tumour of the mouse for two and a half years through nineteen generations, that the importance of the study of experimental cancer was fully realised.

Every one whose experience has been limited to the investigation of human material must have felt dissatisfaction at one time or another with the inconclusiveness of his observations. Too often the nature of a tumour is a matter of mere speculation; we see it in only a single phase of its growth, and have no means of judging of its previous behaviour, or of its future possibilities.

In many cases we can fill the gaps in our knowledge of the life-history of a particular tumour from a series of observations of similar growths, but sooner or later a time comes when, in default of facts, we have to fall back upon theories.

The value of working with a tumour which can be propagated in animals through many generations immediately becomes apparent; we can alter at will the conditions under which it is growing, and we can submit it to examination at any period of its growth. Further, it is only under experimental conditions that we can separate essentials from non-essentials and thereby define the various factors which may predispose to the formation of tumours; while the importance of this method of research in the study of the efficacy and mode of action of palliative and curative measures is obvious.

By prolonged and systematic investigation it has been shown that innocent and malignant tumours occur in the same variety and situations in mammals, birds, fishes, and amphibians as in human beings. This is true of both wild and domestic animals, though the latter, of course, offer greater facilities for examination, and supply the greater part of the material. The natural advantages of the mouse as an experimental animal, its small size, its cheapness, and the ease with which it can be handled, have been taken full advantage of, and its neoplasms have been studied in greater detail than those of any other creature; but it must not be forgotten that cancer is ubiquitous in the animal kingdom

At first these observations naturally met with much adverse criticism, for they strike at the roots of many cherished beliefs as to the influence of such factors as civilisation, diet, environment, and occupation in the ætiology of neoplasms in general and cancer in particular. It became necessary, therefore, to demonstrate beyond all possible doubt the essential similarity between the tumours of mankind and those of the

lower animals. One by one the criteria by which we recognise a malignant tumour in the human being were proved to hold good in the mouse and other animals, and the way was cleared for systematic experimental investigation.

Transplantation is effected by inoculating portions of the spontaneous tumour into other animals of the same species; usually the graft is deposited in the subcutaneous tissues, and for routine work the axilla is the favourite site, but inoculations into muscles, blood vessels, viscera or the peritoneal cavity are equally successful. The graft may be in the form of an emulsion made by mincing the tumour or by cutting it repeatedly with sharp scissors; or small intact fragments may be used, and these give rather better results. Solid fragments are conveniently introduced in a hollow needle of wide bore, fitted with a plunger of such a size that when it is withdrawn a little way it creates a partial vacuum, sufficient to aspirate the graft into the lumen of the needle. For the emulsion, an all-glass syringe graduated in fractions of a cubic centimetre and fitted with a fairly wide bore needle provides a means of delivering with ease an accurate dose.

It is usual to insert the needle under the skin of the groin, and to push it up through the subcutaneous tissues to the axilla before pressing home the plunger. Of course, strict asepsis must be observed throughout the operation.

Should the graft be successful, a tumour which grows progressively develops at the site of inoculation after about ten to fourteen days Sometimes the introduced cells remain latent for a much longer period, and it may be several months before an appreciable tumour forms.

The transplanted tumour behaves in many ways like a spontaneous growth; it infiltrates the body wall, gives rise to lymphatic and vascular metastases, and eventually causes the death of the animal. From it secondary inoculations can be carried out into other animals, and in this way it can be propagated from generation to generation for a period whose limits have not yet been determined.

The successful propagation of a tumour depends upon two factors: the cells introduced, and the soil which receives them. In the first place, the cells must be those of a tumour. Although the cells of normal adult and embryonic tissues may show a transient growth if transplanted into another animal, this soon ceases, and the material introduced becomes absorbed. It is only the tumour cell that is capable of continued and progressive growth.

To obtain successful results, it is necessary to inoculate the living tumour cells Cells which have been disintegrated by repeated freezing

and thawing, or saline extracts of cells, are incapable of giving rise to tumours. The cancer cells are also highly susceptible to adverse influences, and are rendered impotent by the action of moderate heat, by drying, by exposure to radium, and, to a less extent, by the action of various chemical agents. Lastly, the dose administered must be considered, for within certain limits a small dose gives better results than a large one.

It is necessary to realise that the propagation of a tumour is an exceedingly delicate biological experiment in which the influence of the soil may be paramount and is illustrated by the following facts. When a spontaneous tumour is excised and a fragment is replaced under the skin of the animal which bore the tumour (an autoplast) the inoculation is almost invariably successful; failure of the graft to grow is usually due to bacterial infection. Attempts to graft pieces of the same tumour into a hundred mixed stock mice (homoplasts) may give rise to no tumours or to 50 per cent. positive takes. There is a wide variation in the results and it is very rare indeed to obtain 100 per cent. successful grafts. Further it usually takes several generations of transplantation to train a tumour to grow freely in different animals of the same species.

This difference in reaction between the results of autoplastic and homoplastic grafting is explained by the genetic or antigenic differences between animals of the same species. In autoplastic transplantation the graft is of the same genetic constitution as the host; in homoplastic transplantation the graft and the host are different and consequently the host reacts against the implanted cells which, though of the same species, are foreign to the individual. This generalisation is confirmed by the results of transplantation of tumours which arise in inbred homozygous strains of mice, for in these it has been found that transplantation of such tumours within the strain is almost invariably successful.

The tumour cells usually become accustomed to a strange environment after one or two passages, but the early stages of the propagation are often extremely critical. It is the common practice to excise the tumour under anæsthesia, leaving a small portion behind when the wound is closed, or inoculating a fragment into the sound subcutaneous tissue. This fragment often grows with increased rapidity, and offers more favourable material for further attempts at propagation; but in any case it is necessary to inoculate a large number of animals, for the percentage of successes in the first generation is likely to be small

It is the practice in research laboratories to preserve graphic records of the progress of transplanted tumours in the form of silhouettes which

accurately reproduce their measurements and contours. The animals are examined, and their tumours are charted, at stated intervals, usually once a week, and although an enormous amount of labour is thus entailed, it is the only method by which it is possible to see at a glance the rate of growth and the proportion of "takes" in a batch of inoculations, and which will permit of a rapid comparison with the behaviour of previous generations of the tumour. It has been found that tumours have a different ratio of growth, but the growth rate of a particular tumour is fairly constant particularly if it is propagated in a pure inbred strain of animal.

These graphic records, however, can only be applied to tumours which have become definitely established, and it is equally vital to know what happens to the graft before it gives rise to a measurable growth. The immediate effects upon the graft of transplantation to a fresh soil have been thoroughly investigated, and the examination of "early stages," as it is called, has resulted in establishing important principles.

The method consists in the inoculation of a batch of mice with small particles of tumour tissue, sacrificing two or three animals at definite intervals, say 6, 12, 18, 24, etc., hours after inoculation, and submitting the graft together with the surrounding tissue to microscopical examination. Surplus animals are allowed to survive, and their tumours are regularly charted, thereby providing a control on the microscopic findings. It is necessary to observe the most rigid asepsis in order to avoid the introduction of any disturbing element along with the graft; and for the same reason the skin must be epilated before it is punctured with the needle. The whole procedure is extremely laborious, for not only must the various steps in the experiment be carried out with the utmost care, but the grafts themselves must be cut in serial sections, and examined in their entirety.

For a short time after the inoculation no change is visible, but within a few hours there occurs a transient aggregation of leucocytes in the substance and neighbourhood of the graft. This is soon followed by a proliferation of the connective tissue cells in the adjacent areolar tissue, and at the end of twenty-four hours the graft is surrounded by a well-marked zone of fibroblastic reaction. By this time changes also become apparent in the graft itself. The tumour parenchyma remains practically unaltered, but hyaline degeneration can be distinguished already in the supporting stroma. Degeneration of the introduced stroma becomes more and more marked until, at the end of three days, it is extreme. In the meantime the reaction in the surrounding

areolar tissue becomes more pronounced, and from the fourth day onwards there is an active replacement of the degenerated stroma by the connective tissue of the host. Fibroblasts pass in from all sides between the groups of tumour cells, accompanied by outgrowths from the capillary vessels, and eventually, by about the twelfth day, the graft is fully vascularised and supplied with a new stroma from the tissues of the host.

This sequence of events, first followed out in detail in the case of Jensen's mouse carcinoma, has since been shown to obtain with a variety of other tumours, and it may be regarded as established that in the propagation of a malignant new growth it is the parenchyma alone which survives, the introduced stroma being invariably replaced by the tissues of the host. These studies have also shown that the propagated tumour is derived entirely from the parenchyma of the graft, and does not depend in any way upon the initiation of a malignant growth in the corresponding epithelial cells of the host. Finally, it appears that the survival and continued growth of the graft is absolutely dependent upon the provision of a vascularised stroma by the host; in the absence of this reaction, the tumour parenchyma suffers the same fate as the connective tissue, and the whole graft eventually becomes absorbed. There are fundamental differences between a spontaneous and a grafted tumour; the most important are due to the fact that the spontaneous arises from cells which are native body cells, whereas a grafted tumour consists of cells which from the first are "foreign" to the host. The cells of a spontaneous tumour will be unlikely to excite immunological or other response. A grafted tumour in unrelated stocks of animals may well have genetic and chemical qualities unlike those of the cells of the host. They may well be sufficiently foreign to excite reactions leading to the elimination of the graft, and the persistence if not eliminated may account for immunity to further attempts at grafting.

The foregoing description of the propagation of tumours by transplantation applies to the vast majority of tumours, but it is important to note that there are very important exceptions provided by the so-called "filtrable tumours." These are the majority of sarcomas of the domestic hen, a papilloma of the cotton-tail rabbit and an adenocarcinoma of the leopard frog. These tumours will be described later; the point about them to be stressed here is that cell-free extracts of them when injected into appropriate animals give rise to new tumours, strictly new and comparable in all respects with spontaneous tumours.

IMMUNITY AND RESISTANCE

When using the words immunity and resistance in cancer research it must be stressed that they cannot have the full meaning they have acquired in bacteriology. It might have been better if other words had been found for the phenomena described because they are mostly used when a tumour or transplant fails to mature. So far in sera of animals rendered immune to transplantable tumours there has been no satisfactory demonstration of specific cytolysins, agglutinins, precipitins, or other bodies comparable with those developed in bacteriological immunity.

When transplanting tumours it is rare to get a take in every animal and, in some, although the transplant starts to grow, it finally fails and is absorbed. In some of these animals a further attempt may fail and in others all further attempts fail and these animals are said to be resistant. In other animals in which a graft has been established an attempted second graft either of the same kind as the one growing or even taken from the growing graft may fail to take. The tumour giving rise to the resistance continues to grow, but excites a resistance to grafting elsewhere. In some animals this resistance extends to a graft from a different tumour.

In the periphery of human tumours varying amounts of chronic inflammatory reaction are often found. Some workers firmly believe that this is an expression of resistance and is an active reaction to the presence of the growth. There is no good evidence for this. Practically all tumours are in part degenerate and most contain areas of necrosis. It is normal to find a chronic inflammatory reaction in the periphery of non-tumorous dead cells and tissues and it would be strange if this did not happen when the cells or tissues are tumorous.

CELL POLYMORPHISM

To the student of human pathology some of the most interesting phenomena encountered in the propagation of tumours through many generations relate to variations occurring in their histological structure. In the study of human material our investigations are limited to a comparatively brief period in the life history of the tumour; but in experimental cancer there is no such restriction, and it is possible to keep a tumour under observation for many years.

A number of propagable tumours retain their histological characters and transplantability unchanged through many generations; others show during propagation profound alterations in their structure and

biological behaviour. The whole question is one of great complexity, but it is permissible to single out a few of the salient features, since they are of special significance to the general pathologist.

In an ordinary carcinoma of the human breast it is common to find acinous areas mingled with alveoli, and a similar structure may obtain in corresponding tumours of the mouse. In the course of propagation these tumours may exhibit from time to time stages in which the alveolar or the acinous structure becomes more prominent, though there is never any doubt as to the identity of the transplanted with the primary growth. In other cases, however, the histological structure may undergo a permanent change, and acini may be replaced entirely by alveoli.

Other instances have been observed in which a mixed alveolar and acinous structure is combined with areas in which the epithelial cells are so altered as to be almost identical in appearance with those of a spindle-celled sarcoma, but in subsequent generations the sarcomatous-looking cells revert back to the epithelial type.

Even more remarkable are those keratinising tumours which present at one and the same time areas having the typical structure of a squamous-celled carcinoma with prickle cells and keratinisation, along with others having the usual acinous or alveolar histology. The connection between the three types of growth is so intimate that differentiation into squamous cells with keratinisation may appear in one part of a single acinus. After some time the squamous-cell differentiation may be lost, but for several generations the variations in the histological structure may be very pronounced

The recognition that the tumour cell possesses such possibilities in the way of polymorphism should go far to explain some of the anomalous neoplasms met with in human pathology, and should tend to make us somewhat cautious in their interpretation. A broad outlook is essential in so intricate a subject, and if this appears to engender an attitude of undue agnosticism, this is at least a fault on the right side.

In a rather different category are those cases in which the stroma of the growth ceases to play a subsidiary part. Several cases have now been recorded where, in the propagation of a mammary carcinoma, an unusual activity became apparent in the stroma of the growth, eventually resulting in the development of a definite sarcoma. Once the sarcomatous change appears, it rapidly gains the ascendancy and completely replaces the carcinomatous element. By appropriate measures it is possible to propagate both strains simultaneously, or to separate one from the other ; and experiments seem to show that the

age of the carcinoma is the determining factor in inducing the change in the connective tissue.

The condition has also been found in spontaneous tumours of the mouse, though propagation in these cases resulted in the growth of a *pure sarcoma alone.*

So far, the reverse process has not been demonstrated, and no propagable carcinoma has arisen in the transplantation of sarcomatous tissue in the neighbourhood of epithelial organs.

THE EXPERIMENTAL INDUCTION OF TUMOURS

The study of spontaneous and transplanted tumours has yielded results of the first importance and has taught us more about the nature of cancer than we could possibly have learnt in any other way. But it has its limitations, chief of which is that it tells us little or nothing about the initiation of the malignant process. Before we can hope to increase our knowledge in this direction it is necessary that we should be able to produce tumours in experimental animals For a long time all attempts to do this were unsuccessful, but now cancers can be produced at will in a number of animals and by various means. Yamagiwa, Ichikawa, and Tsutsui (1914) were the first to demonstrate the possibility of producing carcinomata of the skin of rabbits and mice by the repeated applications of tar. Their observations were actively followed up by other workers and opened up entirely new fields of cancer research which has resulted in many important observations.[1]

Cancerous Agents. These may for convenience be grouped under (*a*) chemical, (*b*) physical, (*c*) hormonal and (*d*) living or possibly living.

Chemical Carcinogens. The scrotal carcinoma of chimney sweeps was described in 1775 (Pott) and more fully in 1843 (Curling). Since that time the association of various skin carcinomas and tars and tar derivatives has been recognised. In 1914 precancerous changes and carcinomas were produced in rabbits' ears by painting them with tar, and since then many workers all over the world have produced carcinoma by like means especially in mice. Bloch and Kennaway were responsible for showing that the active agents in tars depended on the temperature at which they were distilled and that the carcinogenic substances were hydrocarbons. Following these observations much research has been done on the carcinogenic action of chemical substances, not all of them obtained from tar. Dibenzanthracene, benzypyrene and methylcholanthrene are three of the substances most investigated. It appears

[1] See *Seventh and Eighth Scientific Reports of the Imperial Cancer Research Fund*, 1921–3, where the literature is referred to.

that their carcinogenic activity depends on their molecular structure and it is certain that they are extraordinarily specific in that of two almost identical substances one may be actively carcinogenic and the other not at all. Methylcholanthrene was produced by dehydration of bile acids and is one of the most active chemical carcinogenic agents yet found. This naturally raises the question of the relationship between carcinogenic agents and the similar substances which occur in the body, particularly the sterols. All that can be said at present is that there is no evidence of the occurrence in the body of the sequence of events necessary to change sterols to methyl-cholanthrene.

Susceptibility to chemical carcinogens varies in experimental animals. Some, like the mouse, are good subjects for "tar" painting, others such as the guinea pig, do not respond to painting. The susceptibility to painting is possibly dependent on the degree of permeability of the skin. In animals resistant to painting, tumours may be induced by implanting chemical carcinogenic substances into various parts of the body. The carcinogenic hydrocarbons are mostly insoluble in water so that solvents such as benzene, oils of various kinds or lard have to be used. Painting a surface usually excites a carcinoma, injection into subcutaneous tissues or connective tissues generally excites a sarcoma. For the most part the action is local in both types of treatment except that in some few cases tumours of the lung develop from injections elsewhere. Diet appears to have some influence on the development and growth of tumours in experimental animals There is, however, no evidence that diet has any inhibitory or accelerating affect in man. In animals there is always a latent period between starting the painting or injection and the development of a tumour—in mice this period is about 120 days. This in comparable time or proportion of life in man is about ten years. We now know that in man the carcinomas known to be caused by chemical substances or radio-active substances have a latent period of about ten to fifteen years.

Two chemical carcinogenic substances unrelated to the hydrocarbons are scarlet red (o-aminoazotoluol) and a yellow dye (p-dimethylamino-azobenzine). These, injected subcutaneously or taken by mouth, produce carcinoma of the liver. Orr (1940) observed that degeneration and necrosis of liver cells precedes regeneration and tumorous hyperplasia suggesting that the specificity in production of liver carcinoma is as much related to liver regeneration as to actual liver tumour The sequence of events is degeneration and necrosis of liver cells, fibrosis, regeneration, carcinoma. There are many substances that will produce these changes as far as fibrosis and regeneration. It is suggested that

these two have some extra carcinogenic property which excites the atypical proliferation of carcinoma and not that the natural termination of fibrosis of the liver is carcinoma.

Browning, Gulbransen and Niven (1936), when treating mice inoculated with *T. brucei* therapeutically with a styryl quinoline compound (styryl 430), found that a sarcoma developed at the site of injection of the dye. This substance is water soluble and a single subcutaneous injection excites the production of a sarcoma at the site of injection in from six to twelve months.

Chemically induced tumours are transplantable in the same way as spontaneous tumours and their powers of proliferation are as unlimited. It follows from this that the minute dose of chemical carcinogen which is sufficient to initiate the carcinoma can play no part in the later development of the tumour. In fact it can no longer be recovered after the first few transplants.

Physical Carcinogenic Agents. X-rays, radium and radioactive substances have all been responsible for the production of tumours in man. Excessive exposure to sunlight, heat (as in " Kangri burn ") and in mice exposure to ultra-violet light and repeated freezing of the skin are also claimed to be carcinogenic. Radio-active paint used in the painting of luminous dials in an American factory led to the development of osteogenic sarcoma in those girls who pointed their brushes with their lips, the swallowing of minute doses of the paint being sufficient to make bones in which it was deposited radio-active several years after death. Less laboratory work has been carried out with these substances than with the chemical carcinogens, but all these agents have been successfully used experimentally to produce growths in laboratory animals. Thorotrast (thorium dioxide), a radio-active substance devised for intravenous injection to demonstrate the liver and spleen by X-rays has been shown by many workers to cause tumours in animals. In guinea-pigs, which are normally very resistant to attempts at producing cancers, Foulds, after injecting thorotrast into the base of a nipple obtained four tumours from nine animals. These consisted of one carcinoma and three sarcomata and developed after an interval of thirty-seven months.

Hormones. Internal secretions or hormones are the " chemical messengers " which play a large part in regulating the activities of cells in various parts of the body and therefore directly or indirectly the growth of these cells. It is becoming increasingly clear that the disturbance of one organ of internal secretion disturbs the others. For this reason the apparent action of any given internal secretion on the

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body may be due to changes in a number of glands. So that it is often difficult to sort out the exact part played by each hormone in producing proliferation in any given tissue. This has complicated the study of such apparently simple observations that an excess of ovarian secretion will lead to changes in the epithelium of the breast. But in spite of the difficulties it is now clear that œstrogenic substances in excess may produce (1) epithelial changes in the mammary gland upon which carcinoma may develop in both male and female mice of strains normally having a low incidence of mammary cancer, (2) changes in the endometrium of rats and, after prolonged administration, leiomyomata in the uterus of guinea-pigs and rabbits.

In 1916 Lathrop and Loeb observed that a strain of mice in which the percentage of spontaneous breast cancer was normally high, ovariectomy performed before the age of six months greatly reduced the incidence of breast tumours, and when it did occur in the spayed animals it was at a more advanced age. Ovariectomy after the age of six months had little influence on the tumour incidence ; it was later found by W. S Murray that if the operation was carried out at a still earlier age (under three weeks) spontaneous breast cancer was entirely prevented and that the transplantation of an ovary into males of the same high cancer strain induced cancer of the breast in a small proportion of animals, a condition which under natural conditions is very rare.

With the discovery of the female sex hormones and their subsequent purification and isolation further advances have been made in this direction.

Lacassagne working with an inbred strain of mice (RIII) found that the injection of œstrin in male mice induced cancer of the breast and thus confirmed the observations of Loeb and W. S. Murray The incidence of mammary cancer in the female was unaffected by œstrinisation, presumably because the mouse of the strain used secreted sufficient to affect breast epithelium. The changes in the breast consist of a hyperplastic condition of the ducts with cystic dilatations resembling that seen in adenomatous hyperplasia, and a curious feature is that the whole mammary tissue of an animal is not necessarily so affected.

This action of œstrin in relation to mammary cancer is quite different from that of a carcogenic hydrocarbon of the skin. In the latter, the substance is applied locally and produces its effect locally, in the former, it is probable that the effect is an indirect one, the œstrin producing secondary changes in the other endocrine glands,

which in turn induce the hyperplastic condition of the breast which may undergo a secondary neoplastic change.

The effect of œstrin on the uterus is to produce an extremely hyperplastic cystic endometrium analogous to that seen in "metropathia hæmorrhagica" in women. Certain observers have described infiltrating endometrial tumours in mice after massive œstrinisation, and recently a uterine tumour has developed which was transplantable and produced metastases. It should be emphasised that uterine carcinoma is very uncommon in mice; in addition to the endometrial tumours, leiomyomata have been induced in guinea-pigs These would seem to be hyperplastic rather than neoplastic conditions for they regress when œstrin is withdrawn, but in other characters resemble uterine fibromyomata

Parasitic Origin of Tumours. From the earliest times and in all countries attempts have been made to prove that cancer was due to a parasite of some kind. None of these suggestions has survived critical examination and no parasite of any form has yet been shown to be the cause of carcinoma in man. Parasites have, however, been found in association with cancers both in man and animals. They cannot be entirely ignored in considering the ætiology of cancer although tests, comparable to those applied in bacteriology before a bacterium is accepted as the cause of a given disease, have failed to incriminate any of them.

In Man. Carcinoma of the bladder may arise following an infestation with bilharzia and the incidence of this tumour in bladders so infested is so much greater than in uninfected bladders that the parasite must play some part in the production of the growth. The exact part played by bilharzia is unknown. The probable relationship is that bilharzia excites an inflammatory reaction in the bladder wall and hyperplasia of the bladder mucosa, and that the actively proliferating epithelium is the kind of soil on which carcinoma is liable to develep. A similar relationship may exist between syphilis of the tongue and carcinoma and in the occasional association between tuberculosis and other infections of the lung and carcinoma.

In Lower Animals. In lower animals many tumours have been associated with parasites of various kinds, but with none of them except the viruses is it possible to produce cancers at will by infecting animals. Even the romantic tale of Fibiger's spiroptera and carcinoma of stomach in rats has been shown by Passey and others to be inconclusive. In spite of this, Fibiger's patient and determined search for the parasite among the cockroaches of Copenhagen, his triumph in finding the right

cockroach and the right parasite, and his ability to reproduce his original finding, all form an examplary classical research. Further research suggests that dietary deficiencies played just as important a part as the parasite.

Viruses. Peyton Rous in 1911 found that some tumours of fowls could be propagated by cell-free filtrates. His discovery has been confirmed in laboratories all over the world and tumours can now be propagated by cell-free filtrates with certainty in fowls (Rous and other sarcomas), in rabbits (Shope papilloma) and in frogs (adenocarcinoma of kidney)

The Rous sarcoma was first found in chickens and could be propagated by transplantation, by ground-up, dried and powdered tumour and by cell free filtrates. At first the filtrate was active in barred Plymouth chickens only, but gradually it became more readily tumour-producing and has now been propagated in most types of fowls and even in pheasants. A mass of critical work and experiment has followed Rous's discovery and a great deal of work is still being done with this and similar tumours. It is now established that the Rous sarcoma is a tumour and that it can be propagated by cell-free filtrates. Most workers have found that it has periods when it can only be propagated by transplants and others when its "infectivity" appears to be enhanced. The propagating agent is particulate and is conveniently included *among the viruses*.

When a virus is injected into the dermis of a fowl a tumour can be detected within three days. This immediate response is characteristic of virus tumours. If at this stage the tumour together with a rim of normal tissue is removed the fowl is cured. The action of the virus is thus localised to the cells in the area of injection. The cells first stimulated by the virus are responsible for the cells forming the tumour mass and for an endless succession of cells if the tumour is propagated by transplantation. The virus multiplies with the multiplication of the tumour cells and can be recovered from them at any stage of the tumour growth.

A number of fowl tumours, all of which are transmissible by cell-free filtrates have now been described. They all differ in their histological characteristics, in their local type of growth and in the *distribution* of their metastases. The Rous sarcoma probably arises from fibroblasts (Ludford), another tumour is an osteochondro-sarcoma and yet another is an endothelioma. *Each of these tumours* retains its individuality whether it is propagated by cell-free filtrates or by transplantation. So that apart from the incidental finding that they

can also be transmitted by cell-free filtrates they are very like the mammalian cancers which cannot yet be transmitted except by cell grafting. On injecting a cell-free filtrate into subcutaneous tissues a connective tissue reaction results and in the absence of such reaction a tumour does not develop. If the filtrate is injected intravenously with the minimum of trauma no tumour develops, but if damage leading to connective tissue proliferation is produced anywhere in the bird a tumour will develop at the site of damage. Connective tissues lend themselves to this type of experiment, but it is difficult to mimic the experiments in epithelial surfaces or organs. For this reason it is likely that cell-free transmission will be more easily demonstrated in sarcomata than in carcinomata. It is also clear that intravenous injections will be unlikely to produce tumours

Sarcomas induced by chemical agents in chickens cannot be transmitted with cell-free filtrates. Nevertheless it has been shown that such filtrates provoke the formation of antibodies in rabbits which neutralise filtrates of the Rous sarcoma. The Shope papilloma was first found in wild cottontail rabbits and was transmitted to domestic rabbits by applying ground-up papilloma or filtrate to the scarified skin. In the domestic rabbits with increasing age the papillomas become carcinomatous. As a rule multiple carcinomas arise simultaneously and they metastasise and can be propagated by transplants. With the development of malignancy the virus can no longer be recovered from the tumours However in rabbits that have a carcinoma of this type immune bodies which will neutralise the papilloma virus can be recovered from the blood. These bodies are found in rabbits in which the tumour has been grown by transplantation suggesting that although virus cannot be recovered virus is present.

That some influence may pass from tumorous cells to non-tumorous and excite in them a malignant change was suggested in 1905 by the observations of Ehrlich and Apolant, confirmed subsequently by Bashford, Haaland, Russell and others. They described transplantable epithelial tumours which in course of time excited a sarcomatous transformation of the tumour stroma. This phenomenon only occurs in transplants. In man tumours are sometimes described in which a carcinoma has a sarcomatous stroma and, as has been mentioned earlier, cells in the immediate neighbourhood of some carcinomata appear to be changed from normal to carcinomatous. Although this "influence" has not been proved to be a virus the fact that some tumours can be caused by viruses makes it reasonable to assume that it is. And the failure to isolate a virus from a tumour is not of itself

good enough evidence to disprove the virus theory of the causation of tumours.

This is not the place to discuss the nature of viruses and whether they are living agents or not. There appears to be general agreement that as far as those found in animal tumours are concerned they are particulate. They excite antibody reaction and they progressively increase in amount with the increase of the tumour. In Boycott's provocative and learned discourse on "The Transition from Live to Dead: the Nature of Filtrable Viruses" the suggestion is made that there may well be some intermediate state not quite alive. He grades some of the agents in the following way: (i) the growth-promoting substances from tissues show indirect multiplication but make no other suggestion of life, (ii) Lysozyme would pass for an enzyme except that it can multiply, (iii) the Rous agent.

THEORIES

A large number of hypotheses have been brought forward by different observers, but none is entirely adequate to explain all the phenomena presented by tumorous growth. Sometimes it is evident that the proponents of a hypothesis have no clear conception of the phenomena which they seek to explain. From the general description of tumours which has been given it should be quite clear that cancer is a disease of cells and not of the body as a whole and that many substances or physical agents are capable of exciting cells to the brink of autonomous growth and that when this property has been acquired the agents are no longer required for, and indeed take no further part in, the continuation of the new growth. There is no dispute about this aspect of cancer causation All the discussion, which often excites emotion, is concerned with the explanation of the intracellular or intrinsic cause of autonomous growth. Since all the tumours studied experimentally prior to 1911 are not transmissible by any means except grafting of living cells it appeared to be certain to the pioneers of experimental cancer research that "the histological characters, methods of growth and the absence of specific symptomatology, irresistibly lead to the conclusion that it is not permissible to seek for the causative factors of cancer outside the life-processes of the cells" (Bashford Report of I.C R.F., 1904).[1] Alternatively that "the results point definitely to the necessity of searching for the explanation of the nature and cause of cancer in the minute cell-processes which are responsible for the ceaseless cell division and growth of cancer" (Bashford Report I.C.R.F., 1905).

[1] Imperial Cancer Research Fund Reports

Thus it can be stated that the point of view which has been and is still most widely held is that the explanation of the fundamental feature of cancer (the power to grow independently) is to be sought in some variation from the normal in the cell, due to a complete change of state or function or perhaps to a developmental error and not to a cause which is foreign to the body

Although most of the theories which have been advanced are incapable of withstanding criticism it is wise to consider them since it enables us to survey the work which has been done in the past and to clarify our ideas on the subject.

The theories may be conveniently called intrinsic and extrinsic, the first finding an explanation in alterations of the cell, the second in the presence in the cell of a provocative agent of extrinsic origin.

Intrinsic Theories

1. **Theory of the Alteration of Tissue Tension** (Waldeyer and Thiersch). It is assumed that a state of equilibrium exists between connective tissue and epithelium, each having an exactly balanced controlling influence over the growth of the other. As the result of their earlier senescence, the connective tissues are supposed to lose this control over the epithelium, which, in consequence, proliferates unchecked It is further assumed that, once liberated from control, the epithelium is able to proliferate to an unlimited extent.

This theory is inadequate to explain the infiltrative powers of malignant growths or their powers of forming metastases ; it does not take into account the comparative rarity of multiple malignant tumours, and it absolutely fails to account for the occurrence of sarcomata or of the innocent connective tissue tumours. It has also been shown by tissue culture that it is possible to propagate indefinitely pure growths of epithelial or connective tissue cells without their undergoing malignant change.

2. **Theory of Embryonic Rests.** According to this theory—first enunciated by Durante in 1874 and warmly upheld by Cohnheim—all tumours are supposed to arise in " rests " The principle of this theory has to do with the potentiality of cell multiplication and differentiation. The whole individual is produced from a single fertilised cell. When this cell divides its daughter cells may each produce a perfect individual. Gradually, with their further subdivision this potentiality is lost and in adult life with full differentiation of the cells they can only reproduce their like. Some even fail to do this and others can only do it to a limited extent. Cohnheim's theory postulates that scattered about the

body in organs and tissues are cells which have lain dormant but have retained their embryonic potentialities for growth. These cells or groups of cells are the cell "rests." Such "rests" *may remain embedded in the tissue or organ they were intended to form, or may be* transplanted to different parts of the body; they are capable of retaining their vitality and powers of growth, and, in response to some stimulus, irritation, or what not, of undergoing proliferation, of forming *the neoplasm.*

A wealth of evidence has been adduced in support of this doctrine. Roux, in demonstrating the occurrence of fœtal rests *in the embryo* of the frog, demolished the doubts that were cast upon the existence of such hypothetical aberrant germs; and in *man, nodules of tissue* closely resembling the cortex of the adult suprarenal gland in their structure may often be found on the surface of the kidney, and, more rarely, on the liver, in the broad ligament, and in the spermatic cord. The frequency of malignant tumours at the orifices of the body, where such developmental errors might be expected to occur, the teratomata and the dermoid tumours, and the malignant transformation of nævi, are all points in favour of the hypothesis.

Yet, although a large number of neoplasms are certainly fœtal in nature, this conception does not apply to all, and it will not explain the definite age incidence of carcinoma or the formation of malignant tumours in response to irritation in varied situations where there is no evidence of any such congenital derangement.

Even if this theory be accepted, no explanation is forthcoming as to why such "rests" should suddenly begin to grow after having remained latent for so many years.

3. **Theory of Growth Liberation** (Ribbert). This theory is practically a combination of the preceding ones. Like Cohnheim, Ribbert would ascribe the origin of tumours to "rests," but he claims that these may be "post-natal" as well as fœtal. As the result of long-continued chronic inflammation, he believes that groups of cells are cut off from their normal relationships and become embedded in a strange environment, free from all physiological control, and at liberty to proliferate at will

So in carcinoma of the tongue, for example, it is the chronic subepithelial reaction which is primary; the tumour growth from a group of epithelial cells that has been displaced and cut off from the surrounding epithelium by the connective tissue changes, is secondary.

Ribbert and his followers have studied in great detail the histological changes seen in chronic dermatitis and similar processes, and describe

a definite "pre-cancerous stage" in these forms of inflammation, but their interpretation is not accepted by all authorities. The difficulties in the way of determining the stage when epithelium is about to become malignant are, of course, quite obvious, and often the inflammatory changes in the connective tissue appear to be secondary to the tumour rather than the cause of it.

Conditions favourable to the production of malignant tumours, according to this conception, exist as a rule in the healing of wounds, yet tumour formation in these cases is the exception. Again, the limitations of growth seen in the transplantation of normal tissue grafts is inconsistent with the theory. Finally, this explanation is adequate only for the carcinomata, and does not apply to the sarcomata.

4. **Habit of Growth Theory.** Reference has already been made to the anaplastic character of new growths, to the lack of differentiation exhibited by their cells. This property is such a striking feature of tumours, especially in those of the malignant type, that it has been the subject of much study and speculation, and attempts have been made to elucidate the ætiology of cancer by defining the cause of the anaplasia.

Working on these lines, Adami has elaborated his theory of the habit of growth.

He holds, in the first place, that the metabolism of the cell is controlled by the nucleus which plays the predominant part, not only in proliferation, but also in the performance of function ; and that in the fully differentiated cell, under normal conditions, practically all the available energy is used up for the purpose of work, leaving little or none for proliferation or growth. The two processes are absolutely antagonistic to one another, and it is only in the undifferentiated cell, or in the fully developed cell which has undergone retrogression, that growth takes precedence of function. He also points out that, by virtue of inertia, the adult cell tends to maintain its state of functional activity and shows little proliferative power. If, however, as the result of some external influence it is forced to undergo frequent divisions then, because of the same inertia, it will continue to divide and will lose its habit of work.

Adami, then, would regard tumour formation as being in the nature of a reaction on the part of the cell to some external influence acting upon its normal metabolic processes. Either as the result of long-continued cell destruction, or from an alteration in the character of the food supplied to the tissues, growth gradually supersedes functional activity until it becomes the dominating feature. This theory opens up many possibilities, but it fails to solve the essential question.

Chronic irritation and destruction may exist for years without inducing the habit of growth in the cell, though the tissues must be in a state of constant reproduction ; and we have no *indication as to why this vital* change should occur.

5. **Biological or Reproductive Theory.** This theory, associated with the names of Farmer, Moore, and Walker, depends upon the recognition in malignant growths of mitoses of the reproductive type (heterotype mitoses). Mitosis, or cell division, is of two types according to whether the cell is destined to form part of the body tissue, or whether it is to become a reproductive element.

In the division of the somatic, or body cells, the chromosomes have a V-shape, and are arranged at right angles to the spindle, splitting longitudinally. In the heterotype mitosis which occurs in the reproductive cells the chromosomes are thicker, have a ring or loop form, and split transversely, being arranged longitudinally in the spindle. Further, in the heterotypical mitosis the number of chromosomes is *half that found in the somatic type, in order to allow of the restoration* to the normal number after conjugation has occurred between the male and female elements. Professor Farmer and his colleagues have observed such heterotypical mitoses in many forms of malignant growths, and regard the malignant process as being due to a conversion of somatic cells into the reproductive type. Other observers, however, have not been able to confirm these findings, and it should also be noted that the theory can only apply to malignant growths, since in innocent tumours the somatic type of mitosis always obtains.

6. **The Induction of Somatic Mutation.** Changes in the chromosome complex of germ cells are capable of giving rise to new transmissible characters in the offspring ; these are called mutations It has been [illegible] might account for

evidence that apart from sex cells mutation can occur in the body cells and it is upon this possibility that the theory rests and is called the somatic mutation theory. Bauer suggests that multiple exostoses, polyposis coli and xeroderma pigmentosum are examples of this condition which are hereditarily transmissible. It is well known that cancer develops with exceptional frequency in the second and third of these conditions.

In order that a cancer cell mutation could arise it would be necessary for the cells concerned to be in an active state of cell-division. Most of the known carcinogens cause cell and tissue damage leading to regenerative activity. So that the necessary conditions are present

for the development of alterations in the gene mechanism of somatic cells And this possibility does not exclude other ætiological factors which will excite cell proliferation or during cell division might act upon the chromosomes inducing alterations in the genes, which might be transmissible. Bashford, Murray and, more recently, Ludford have shown that in transplantable tumour cells there is variation both in shape and number of chromosomes, but enough is not yet known about the mechanism of normal or abnormal cell division to warrant the acceptance of this theory. And it appears inadequate to explain the origin of spontaneous tumours because a succession of mutations would be necessary and mutations in general destroy cells It is possible that the variations in chromosomes is an expression of cell disorganisation consequent on tumour development and not an indication of its cause.

7. **The Senescence Theory.** There is some biological evidence that unicellular organisms continuing to multiply by simple fission tend to produce degenerated and atypical forms. The underlying idea in the senescence theory is that there is a mathematical limit to the number of times cells can divide and that when that limit is reached they can only continue to grow by atypical and abnormal cell division. Under normal conditions the number of normal divisions is far more than enough for the requirements of the body living for the normal time. If, however, as a result of irritation from any cause, the cells multiply at an abnormal rate then the total of normal divisions might be exhausted before the death of the individual and abnormal divisions might result. This theory brings together the usual age incidence, association with continued cell proliferation and long lag period between stimulation to proliferation and the development of carcinoma. It fails if applied to chorion carcinoma and other tumours arising in either the fœtus or infancy. There is also evidence in tissue culture that cells can continue to subdivide without sexual phase and without developing any abnormality, for a time much greater than the life of the animal from which they have been derived.

Extrinsic Theories

Since the earliest times cancer has been looked upon as being of the nature of a parasitic disease. Now biologically, all tumours are parasites on the organism bearing them, since they live at the expense of the host with an absolute lack of regard for its physiological needs. But it is not in this more general sense that the term is used, for there is a widespread belief among the laity in the infectivity of malignant disease.

It is obvious that a certain resemblance exists between a known infectious disease, such as tuberculosis, and a malignant new growth; but, as has already been said, the processes are essentially different, and there is no true analogy between the two cases.

A somewhat stronger argument may be advanced in the coccidial disease of the rabbit. Rabbits are frequently found to harbour a protozoon, the coccidium oviforme, which affects especially the liver. Here it is found in the bile ducts, lying free in the lumen or embedded in the epithelial cells. The ducts become generally dilated, the epithelium proliferates and projects inwards in a papillomatous fashion, and, in the older foci, there is a considerable amount of overgrowth of the surrounding fibrous tissue resulting in the formation of a definite capsule, the whole nodule having the appearance of a papilliferous cyst-adenoma. Here, however, the likeness to true tumour formation ceases; the process is really more in the nature of a catarrhal inflammation, the epithelium proliferating in response to a definite irritation, and never assuming neoplastic characters.

In the literature of a few years ago many examples are recorded of the supposed transference of the disease from one person to another. The infection has been ascribed to actual contact with the individual, as in the case of a healthy person nursing a cancerous patient through a prolonged illness, or is said to have been spread by means of utensils, such as drinking vessels, or soiled dressings and clothing. But comparatively few of these cases will bear examination. In many of them the evidence is incomplete, and rests entirely upon clinical observation, and in all of them the same fallacies are to be noticed as in the statistics of "cancer houses."

Further, in direct contradiction to this doubtful evidence we have the fact that no undue liability to cancer has ever been shown to be present among surgeons, nurses, or pathologists whose professional duties would expose them constantly to infection.

The demonstration of a micro-organism invariably present in tumours, and capable of reproducing experimentally the histological characters of the growth from which it was derived, would, of course, have settled the question. And at one time or another almost every variety of micro-organism has been associated with the ætiology of neoplasms. Micrococci, bacilli, blastomycetes and protozoa, all have had their advocates, but none has stood the test of criticism Indeed, rather has the variety of the parasites tended to increase the scepticism of the opponents of this theory. The one which has given rise to greater controversy, perhaps, than any other is the Micrococcus

neoformans, a coccus closely allied to the Staphylococcus albus, described by Doyen as occurring in non-ulcerated tumours and as being capable of giving rise to true neoplasms on inoculation into animals. But more extended investigations have shown that many non-ulcerated tumours are quite sterile, and even when bacteria can be cultivated from them, in only a certain proportion of cases does the organism bear any relation to the Micrococcus neoformans. And no other observer has been able to produce more than simple granulomata in animals by the inoculation of pure cultures of the coccus. The same criticisms apply to the other parasites mentioned above: the impossibility of demonstrating their presence in tumours except occasionally, and the failure to produce with them experimentally anything resembling a true neoplasm.

A careful histological examination of carcinomata will often reveal the presence of small extra- or intra-cellular bodies of a definite form, and with different staining reactions from the cells of the tumour. An extracellular form consisting of round bodies, often arranged in groups, and staining deeply with fuchsin, was described by Russell, who regarded them as being blastomycetes. Other observers have found somewhat similar intracellular bodies, situated in the cytoplasm, and sometimes compressing or displacing the nucleus, and these have been looked upon as forms of an intracellular protozoon. These bodies, however, are not peculiar to neoplasms, but may be found in inflammatory conditions, and it is now generally accepted that they are degeneration products occurring in the cell, or nuclear extrusions into the cytoplasm.

The Virus Theory

Of all agents which might be responsible for tumour growth the only ones likely to do so would be minute intracellular particles which multiply at a rate corresponding to the multiplication of the tumour cells. Such agents have been demonstrated in the group of virus tumours. And there are no characteristics of other tumours which would exclude the possibility that they too had been caused by viruses. It must be admitted that tumours in which a virus cause can be demonstrated are exceptional, but it is not seldom that great progress in the understanding of natural phenomena can be traced to the study of the exceptional. It is therefore important that filtrable tumours should be studied exhaustively and that knowledge so gained should be set in just perspective to the problem as a whole.

It has already been stated that the only tumours which can be propagated by injections of cell-free filtrates or of dried tumour tissue

are sarcomas of the domestic hen, a papilloma of the rabbit and an adenoma of the leopard frog In addition the leukæmias of the domestic hen are similarly transmissible by cell-free filtrates.

Many types of filtrable tumour have been described in the chicken; in addition to the Rous sarcoma they include spindle cell sarcomas, osteochondrosarcomas, rhabdomyosarcomas and endotheliomas Each variety of tumour has its own mode of growth, slow or rapid, and its peculiarities in sites of formation of metastases. For instance, the metastases of the Rous sarcoma are most often found in lungs, liver and heart; those of the endothelioma (Mill Hill 2) appear in the spleen and the remnants of the thymus. Some of the tumours grow with astonishing rapidity; for example the Rous and the Fujinami sarcomas often kill their hosts in ten to fourteen days; others such as the endothelioma (Mill Hill 2) seldom kill in less than four to five weeks and a filtrable fibro-sarcoma (Mill Hill 1) rarely kills the host in less than six months and often continues to grow for a year before the animal dies from widespread metastases.

The filtrate of each hen tumour is active only in hens and is capable of giving rise only to tumours of the same histological type as that from which the filtrate was prepared. From this it is clear that the filtrable agent is extraordinarily specific for both species and cell type.

Attempts have been made to explain the phenomenon of filtrability by suggesting that the agent which passes the filter is an ultramicroscopic malignant cell. This attempt to reconcile filtrability of a few tumours with non-filtrability of the great majority has been shown to be false.

There are a few exceptions to some of the generalisations given above. The Fujinami sarcoma agent is capable of infecting connective tissue cells of the duck, especially of the variety Khaki Campbell, as well as of the chicken, and the agent of the Rous sarcoma infects the cells of pheasants.

The tumours forming the group of filtrable tumours do not differ in any respect from any other group of tumours except in being transmissible with cell-free filtrates.

It might be argued that the agents are in fact produc d by the tumour cells and are native body products. Against this view must be set the fact that the filtrable ultra microscopic agents are antigenic and evoke the formation of neutralising antibodies and agglutinins in the horse, goat, rabbit, goose, duck and chicken. The antibody formation in the chicken suggests that the agent is not fowl protein, but is of extrinsic

The Riddle of Cancer. C. Oberling, 1944. Oxford University Press.

origin The exact nature of the agent is less important than the effects it produces and in our present state of knowledge it is conveniently classified as a virus. If this is the correct interpretation of our knowledge it must be concluded that a typical group of sarcomas are caused by an extrinsic viral agent.

It has been proved that a neutralising antibody prepared by injecting the virus derived from one tumour, for example the Rous sarcoma, is capable of neutralising the virus both of the Rous sarcoma and the virus of dissimilar tumours such as the endothelioma. It is clear therefore that if the viruses are not identical they are closely allied antigenically. The only evidence supporting different viruses is that virus derived from each type of tumour will only give rise to tumour of similar histological type It is not impossible that identical viruses might give rise to different types of tumour.

It is probable that like many bacteria, especially the anaerobes, viruses are highly conditioned in their activity and induce tumour formation only under very special conditions

Our knowledge is at present too meagre to warrant an emphatic statement involving a wide generalisation linking the intracellular activity of viruses with tumour growth in general It is possible that Bittner's milk factor, which plays a fundamental rôle in the genesis of mammary cancer, may open new chapters in our knowledge and bridge the gap which at present separates the filtrable from the general mass of tumours.

The most attractive features of the virus theory of cancer are that there is a factual basis for the theory and that as a working hypothesis it continues to yield fresh knowledge.

SUMMARY

Cohnheim's theory of cell rests may apply to teratomas, teratoblastomas and tumours arising in ectopic cells, but does not explain how these dormant cells are roused to tumorous proliferation. The association of carcinoma with various precancerous conditions such as chronic inflammations, atypical hyperplasias, benign new growths and occupational chemical and physical carcinogens is established. But the effect of all these appears to be to bring the cells to a potentially cancerous condition and some further change or agent is necessary to make them actively cancerous. It is suggested that mutations may arise in the cells themselves as a result of their unusual activity. The chemical relationship between carcinogenic hydrocarbons, vitamin D, bile acids and hormones supports this possibility. The chemical

carcinogens having initiated the process appear to take no further part in the development of the tumour.

Needham has suggested a unifying hypothesis, namely: As the result of various non-specific factors—heredity, endocrinal imbalance and the exposure to external carcinogenic agents or an analogous substance produced by the changes of metabolism associated with ageing—certain cells undergo an irreversible somatic mutation with the production of malignant growth which is no longer subservient to the organising influence of the tissues. The hypothesis suggested, though it is in keeping with the experimental findings, leaves much unsolved as to the essential change that takes place in the transition from normal cell regeneration to malignant growth.

The virus hypothesis is attractive and has the very strong support that viruses are the only substances discovered so far that can produce specific tumours at will, increase with the increase of the tumour and can be recovered from it after unlimited propagation either by virus inoculation or tumour transplants. It has to be admitted that in man no virus or similar agent has yet been recovered, nor have they been from the majority of spontaneous tumours in laboratory animals except fowls. This failure is gradually being reduced in laboratory animals, but generally by the finding of new tumours and not by the recovery of virus from established tumours. It is suggested that it is a matter of technique and that some hitherto untried method may ultimately be found which will bring about the separation of the virus from its tumour cells.

PART II

THE GENERAL PATHOLOGY OF TUMOURS

TERMINOLOGY AND CLASSIFICATION

THE terminology adopted in the study of tumours is in a considerable degree of confusion. The term Tumour applies to any swelling, and although among pathologists it has a more restricted meaning, clinicians still employ it in its older sense, and apply it to inflammatory swellings, collections of fluid, and simple hypertrophies as well as to true autonomous tumours.

We are therefore in need of a more distinctive term. "Neoplasm," and its English equivalent, "new growth," are somewhat cumbersome, and although their application is more limited by convention, they are still used in connection with other varieties of tissue production. Teratoma and Blastoma are gradually gaining acceptance, but it is doubtful if the custom of years will ever be broken down, and the various terms are used indiscriminately.

A Teratoma is a tumour derived from totipotential cells, that is to say, cells capable of giving rise to all the tissues of the body.

A Teratoblastoma is a tumour arising from pluripotent cells which can differentiate to produce two kinds of tissue such as epithelium and connective tissue, both types of cells being tumorous and arising from the same parent cell.

A Blastoma is a tumour arising from unipotential cells, cells capable of forming only one variety of tissue. Blastomata are, for the most part, autochthonous, but one form, the chorioncarcinoma, is heterochthonous, since it is derived from fœtal or foreign cells.

The majority of innocent tumours are named from their constituent tissue, the termination *oma* being added; and custom has sanctioned the use of both the classical and the English forms of the plural, so that it is equally correct to speak of fibromas and fibromata.

The malignant epithelial tumours are classed together as Carcinomata, and, similarly, the malignant connective tissue tumours are called Sarcomata.

The terms **Typical** and **Atypical** demand some explanation. By some authors they are used to express innocency and malignancy.

Thus, a tumour composed of fibrous tissue may be either innocent or malignant, a fibroma or a fibrosarcoma. In the former case its structure closely resembles that of normal fibrous tissue, and it is said to be **typical**; in the latter, the structure of the tumour and its constituent cells show marked variations from normal fibrous tissue, differences which are reflected in its mode of growth, and in consequence it is described as being **atypical.** By others the words are used to qualify a tumour, not with reference to the normal tissues, but to other forms of the same class of growth. So we may speak of a typical squamous carcinoma, meaning a malignant growth derived from squamous epithelium, which resembles in its characters the majority of the tumours derived from similar tissues.

Various other terms are in use, but many explain themselves, and we may with advantage leave the consideration of the remainder until the necessity for their use arises.

CLASSIFICATION

So many varieties of tumours exist, and transitional forms are so numerous, that the task of arranging them in an orderly classification is no easy one.

To be of real value such a classification should not only group tumours according to their general structure, but should also indicate their physiological and biological relationships to one another, so that if we are able to place any particular neoplasm in its proper division, we may have some indication, at least, of its biological properties.

Attempts to achieve this ideal have been only moderately successful, for in their mode of growth and clinical behaviour tumours are subject to even more marked variations than they are in their anatomical features.

Any scheme of grouping, therefore, must be of the nature of a compromise if it is to remain of reasonable length.

The subject has been approached from two different points of view, the histological, and the embryological or histogenetic, both of which have their advantages and disadvantages. In the histological classification attention is directed solely to the type of cell or tissue of which the growth is composed, and tumours are arranged according to the corresponding elements from which they arise In the embryological system the tumours are traced back beyond their corresponding adult tissues, and are grouped according to the varieties of immature

or undifferentiated cells which give origin to the fully developed tissues of the body.

Very early in the development of the embryo the individual cells are marked out to form the different organs and tissues of the body, and for this purpose are endowed with certain characteristics. Provided that they remain in their normal relationship to the other cells of the embryo, and are subjected to no adverse influences, they will eventually give rise to structures having definite functions and possessing a constant histological formation. If, therefore, we can with certainty refer a tumour to any particular class of embryological cell, we should be able to hazard an opinion as to its probable behaviour and mode of growth. For this reason the histogenetic classification is, theoretically, the more scientific. In practice it is not so helpful as might be supposed, and, moreover, has to be combined to a greater or less extent with histological systems; nevertheless it opens up many lines of thought, and is undoubtedly conducive to a broader outlook than any purely morphological classification.

But it must not be forgotten that any scheme based upon embryological studies rests to a considerable degree upon a foundation of theory. Until we possess a more exact knowledge of the development of the body, we may come to adopt entirely false conceptions as to the nature of many neoplasms by a too slavish adherence to considerations of cell activity.

Therefore, although a combined morphological and histogenetic classification appears to be the most scientific, it is well to bear in mind also those which depend on morphological characteristics alone.

Of the various histological classifications, possibly the simplest and most satisfactory is that devised by Powell White.[1] This author divides tumours into three main classes, Organomata, Histiomata, and Cytomata, according to whether they consist of organs, tissues, or cells; and the second and third groups are subdivided as often as may be necessary in order to permit of distinction between the various types of tissues and cells which may be represented.

Thus, a cyst of the ovary containing skin, hairs, and glands, that is to say, organs or rudiments of organs, would be placed among the organomata, a tumour composed of atypically arranged tissues, epithelial tubules with a supporting stroma but with no definite glandular arrangement, for example, is a histioma; while a tumour made up of cells which form neither organs nor definite tissues is a cytoma.

[1] *The Pathology of Growth*, "Tumours." London, 1913.

We have, then, the following Table :

A Organomata, or Organ Tumours.

1. Teratoma.

B. Histiomata, or Tissue Tumours.

(*a*) Desmomata, or supporting Tissue Tumours :

1. Myxoma	arising from	myxomatous tissue
2 Fibroma	,, ,,	fibrous tissue
3 Lipoma	,, ,,	fat.
4. Chondroma	,, ,,	cartilage.
5 Chordoma	,, ,,	notochordal tissue
6. Osteoma	,, ,,	bone
7 Odontoma	,, ,,	dentine
8 Glioma	,, ,,	neuroglia

(*b*) Neuromata, or Nerve Tumours.

1 Neuroma arising from nervous tissue.

(*c*) Myomata, or Muscle Tumours

1. Rhabdomyoma	arising from	striated muscle
2. Leiomyoma	,, ,,	smooth muscle

(*d*) Lymphomata, or Lymphoid Tissue Tumours

1 Lymphoma	arising from	lymphoid tissue.
2 Myeloma	,, ,,	bone marrow

(*e*) Epithelial and Endothelial Histiomata.

1 Papilloma
2. Adenoma
3 Angeioma.

C. Cytomata, or Cell Tumours.

(*a*) Blastocytomata	arising from	indifferent cells
(*b*) Sarcomata (desmocytomata)	arising from	supporting tissue cells
(*c*) Neurocytomata	arising from	nerve cells.
(*d*) Myocytomata	,, ,,	muscle cells
(*e*) Lymphocytomata	,, ,,	lymphoid cells.
(*f*) Carcinomata	,, ,,	epithelial or endothelial cells

This Table has certain obvious advantages. It is short and easy to remember. The Histiomata and the Cytomata correspond respectively to the two main groups, the innocent and the malignant, which alone have any real clinical significance. Apart from this, there is certainly nothing in the classification itself to indicate the biological properties of any particular tumour. But these are best learnt by experience; indeed, only an intimate acquaintance with the subject, the result of years of study, can warrant an authoritative opinion in this respect with regard to a large proportion of individual neoplasms It has, however, this great disadvantage. It depends for its success on an accurate interpretation of histological appearances, at which it is not always possible to arrive. In the first two groups there is seldom much difficulty in determining the histological structure of the tumour, but

with regard to the cytomata it is, in some cases, by no means easy to decide upon the type of cell of which the growth is composed. This is specially noticeable in respect to the hypernephromata, the melanomata, and certain other varieties; and the necessity for adopting a dogmatic attitude with regard to these in the absence of any exact knowledge as to their nature, constitutes a serious drawback. Moreover, the endotheliomata often differ so widely in their structure from the cytomata derived from epithelial cells, that it is scarcely justifiable to include them both under the heading of Carcinomata.

Turning to the Embryological classifications, we find that the older forms were based on the recognition of three primitive orders of cells forming the epiblast, hypoblast, and mesoblast of the embryo, and three varieties of tumours were described according to their supposed origin from derivatives of one or other of these layers. But very obvious difficulties soon became apparent. For example, many tumours of the central nervous system were placed in the epiblastic group, though they differ widely in their histological features from other tumours of epiblastic origin, resembling more closely the mesoblastic, or connective tissue growths. Again, undoubted glandular tumours are found in the kidney, an organ of mesoblastic origin though having a glandular structure.

Modern research, however, has done much to clear away these anomalies, and, utilising the results of more recent studies, Adami has suggested a classification which has many features to recommend it. He points out that each of the three primitive layers of the embryo gives rise to two orders of cells, those forming "lining membranes," and those forming solid tissues or "pulps." Thus, not only does the epiblast form the covering epithelium of the body and the structures immediately derived from it, but an ingrowth of it develops into a solid structure, the central nervous system. And the hypoblast gives rise to solid "pulp" tissue in the notochord, as well as the lining membrane of the alimentary canal, and outgrowths from it such as the liver and pancreas.

In the mesoblast, which is composed of cells derived from both epiblastic and hypoblastic layers, a similar differentiation is observed. It divides into two portions (1) the mesothelium or lining membrane of the primitive body cavity, and (2) the mesenchyme, or body mass. From the mesothelium are developed organs such as the kidney and suprarenals, as well as the lining membranes of the serous cavities, and also solid outgrowths which become the myotomes, giving rise to striated muscle. From the mesenchyme are formed the connective

tissues of the body, and also lining membranes, in the endothelium of blood and lymphatic spaces.

Developmentally, then, the cells of the body may be divided into two main types:

(*a*) The "lining membrane," "rind," or "lepidic" cells, and (*b*) the "pulp," or "hylic" cells.

Cells of lepidic tissues are in close apposition to one another, and are not separated by any intercellular tissue, their nutrient vessels being contained in a coarse hylic tissue stroma. Cells of hylic tissue, on the other hand, are separated from one another by an intercellular substance, and the nutrient vessels tend to lie in close contact with them

With this embryological basis Adami divides tumours into two main groups: (1) Lepidomas, arising from lepidic or lining membrane tissues, and (2) Hylomas, arising from hylic or pulp tissues. Further, the Lepidomas are divided into two classes, (*a*) Primary, and (*b*) Secondary, or Transitional, according to whether the cells have descended directly from the original epiblast or hypoblast, or whether they have passed through a mesoblastic stage.

His full classification is as follows:

I. Lepidic, or Rind Tumours

A. Lepidomas of the First Order

1 Of Epiblastic Origin

(*a*) Typical. Papilloma, epidermal adenomata (of sweat, salivary, sebaceous, and mammary glands, etc)

(*b*) Atypical: Squamous epithelioma, carcinoma of glands of epiblastic origin

2 Of Hypoblastic Origin.

(*a*) Typical. *Adenoma and papilloma of digestive and* respiratory tracts, thyroid, pancreas, liver, bladder, etc

(*b*) Atypical: *Carcinoma developing in the same organs* and regions.

B. Lepidomas of the Second Order, or Transitional Lepidomas.

3 Of Mesothelial Origin..

(*a*) Typical. Adenoma of kidney, testicle, ovary, urogenital ducts, adenoma of uterus and prostate, adenomas originating from the serous membranes, "Mesotheliomas" of pleura, peritoneum, etc

(*b*) Atypical Cancer of the above-mentioned organs, squamous endothelioma, so called, of serous surfaces, epithelioma of vagina, adrenal mesotheliomas, hypernephroma

4. Endothelial Lepidomas

Tumours originating from the *endothelium of the* blood and lymph vessels, lymphangeio-endothelioma, hæmangeio-endothelioma, peritheIioma, cylindroma psammoma, *cholesteatoma.*

II. Hylic, or "Pulp" Tumours.

1. Of Epiblastic Origin.
   (*a*) Typical: True neuroma, glioma
   (*b*) Atypical: Gliosarcoma.

2. Of Hypoblastic Origin.
   Chordoma.

3. Of Mesenchymal Origin.

   A. Mesenchymal Hylomas.
      (*a*) Typical: Fibroma, lipoma, chondroma, osteoma, myxoma, leiomyoma, angeioma, myeloma.
      (*b*) Atypical: Sarcoma with its various subdivisions—Fibrosarcoma, chondrosarcoma, lymphosarcoma, angeiosarcoma, etc., of origin still debated, melanosarcoma.

   B. Mesothelial Hylomas.
      Rhabdomyoma

It will be seen that only the autochthonous blastomas are considered in this table; the teratomata and the heterochthonous blastomas receive separate treatment.

The classification is somewhat unwieldy, and suffers also from the disadvantage that it entails the introduction of a fresh nomenclature in a subject already overburdened in this respect. Nevertheless it is in many ways, superior to all other systems.

It is complete in so far as it accommodates almost every type of tumour, and it avoids the difficulties arising from an imperfect understanding of histological details which are inherent in all morphological classifications.

It is, of course, a classification largely based on theories, and may, in the future, require modification in some respects. It agrees, however, with the known facts, and, above all, it helps us to appreciate and compare the relationships of the various blastomas from a biological as well as a morphological standpoint.

One of the most successful features of the scheme is the recognition of the great subclass of Transitional Lepidomata.

Certain tumours of this class, especially the endotheliomata and hypernephromata, show a bewildering variation in their histology, at one time being distinctly carcinomatous in structure, at another approaching the sarcomatous type. There has been infinite speculation as to their nature, but Adami's conception offers a reasonable explanation of the pleomorphism so characteristic of them. When growing slowly these tumours may behave as adenomata or carcinomata, but

when growing rapidly they tend to lose their lepidic character—in obedience to the law that the properties which have been last acquired are the first to be lost—and assume the structure of the older hylic tissues.

Although this system is more scientific and suggestive than any other with which we are acquainted, yet, as Adami acknowledges, it is scarcely suitable for everyday use. From the clinical standpoint we have achieved a great deal if we can distinguish between the innocency and malignancy of any particular blastoma; this, together with the name of the tumour, or possibly a compound name indicating its structure, will fulfil all ordinary requirements.

In the description of the types of tumours which follows, the older nomenclature will be adhered to, and although all the more important varieties will be treated of, they will be grouped as convenience suggests, and in some cases their consideration will be deferred until we come to deal with the organs in which they usually occur.

For purposes of description we may divide tumours into the following groups:

The Innocent Connective Tissue Tumours
The Sarcomata, or Malignant Connective Tissue Tumours.
The Innocent Epithelial Tumours, Papilloma and Adenoma.
The Carcinomata, or Malignant Epithelial Tumours.
The Tumours of the Nervous System.
The Melanomata
The Endotheliomata.
The Teratomata.

THE INNOCENT CONNECTIVE TISSUE TUMOURS

FIBROMA

A Fibroma is a tumour derived from fibrous connective tissue, and is therefore of very wide distribution. Almost every part of the body may be the seat of fibrous growths, but the majority of these tumours are found in connection with the skin and subcutaneous tissues, nerves, the sheaths of muscles and tendons, and in loose, submucous connective tissue. Though they are less common in other situations they are not infrequently encountered in solid organs such as the uterus, ovary, kidney, and breast.

The fibromata are innocent tumours, growing slowly and expansively; they are sometimes multiple. In solid organs they compress the

surrounding tissues, forming capsules from which they can be shelled out; but when growing in the wall of a hollow viscus they have a tendency to project into the cavity as pedunculated polypi. This is particularly the case with the subcutaneous fibromata and with those of the uterus and the alimentary canal. As a rule, these tumours are covered by a layer of tissue derived from the organ in which they grow, but as the result of ulceration this investment may be absent, in which case the superficial layers of the polyp present a well-marked inflammatory reaction.

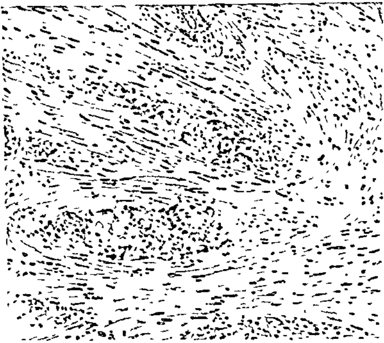

FIG. 15. *Fibroma of the breast. The tumour is composed of interlacing bundles of fibrous tissue, some of which are cut transversely.*
Obj. 8 mm apochrom. Comp. oc. 4 Tube length 160 mm

Macroscopically, fibromata form rounded, lobulated tumours varying considerably in consistency; some are extremely dense and firm, while others are softer and more yielding. On section the harder forms are extremely tough, and the cut surface has a white, glistening, whorled appearance often likened to "watered silk." The soft fibroma cuts much more easily, and the section is looser and more homogeneous; it is often moist and œdematous, and may show jelly-like areas of myxomatous change.

According to their consistence, then, two types of fibroma may be distinguished: (*a*) hard fibroma, and (*b*) soft fibroma, but intermediate

forms are extremely common, and the same tumour, even, may vary in consistence in different parts. At its best the distinction is somewhat artificial, and the soft variety often owes its peculiar character to degenerative changes rather than to true differences in structure.

Microscopically (Figs. 13 and 14), fibromata consist of fibroblasts and bundles of formed fibrous tissue, and occasionally contain a few elastic fibres. There is a delicate stroma of connective tissue separating the lobules of the growth, and in it run the nutrient vessels. These are usually badly formed, and may consist of little more than a tube of endothelium surrounded by a dense connective tissue coat.

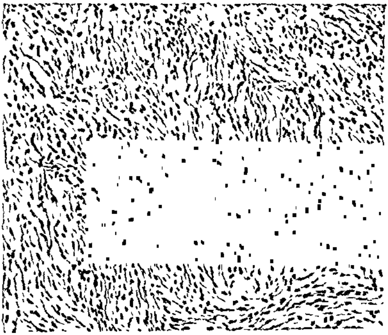

FIG. 14. Fibroma of the ovary.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length 160 mm.

In the hard fibroma there is an abundance of formed fibrous tissue arranged in interlacing bundles, or as a dense felt-work, and the cells are compressed and comparatively few in number. The soft fibroma contains less formed fibrous tissue and is more cellular. Its tissue spaces are wider, and there is often an excess of œdema fluid. Rarely, multinucleated fibroblasts or giant cells may be met with in the soft tumours, but, when present, these generally indicate that the growth is more of the nature of a fibrosarcoma than an innocent fibroma.

Fibrous tissue enters into the composition of many compound tumours forming, among others, fibro-adenomata, fibrolipomata, and fibromyomata. But apart from these true mixed blastomas, other

tissues are met with in fibromata as the result of degenerative changes. Thus the hard fibromata are liable to undergo hyaline and calcareous degeneration, while the soft variety may show a tendency to myxomatous and, more rarely, fatty degeneration.

Closely allied to the fibromata, though differing from them in important particulars, are certain conditions of fibromatosis or fibrous tissue overgrowth. In some organs—the kidney, the prostate gland, and the breast—we may encounter localised areas of fibrous tissue growth forming tumour-like nodules, which, however, are not encapsuled, but gradually fade off into the surrounding tissue. They are frequently multiple, are of slow growth, and often contain glandular elements which have become incorporated in the mass in the course of its growth. In both the breast and prostate they are probably the result of endocrinal dysfunction. Rarely, a sarcomatous change may become apparent in one or more of these nodules, though this is always a late phenomenon.

Similar blastomatoid growths are met with in connection with other tissues of the body, and only by a careful examination is it possible to distinguish them from true blastomas

In the conditions known as **keloid** we have an instance of this process as it affects fibrous tissue, which is of sufficient importance to merit a more detailed consideration.

Keloid is the name given to an excessive production of cutaneous fibrous tissue, usually in association with some form of irritation, or at the site of injuries or operation wounds. Firm plaques or ridges are formed, having smooth, shining surfaces and sharp margins from which pointed processes extend into the neighbouring skin. As time goes on the tumours become harder and only increase in size very slowly if at all There is a striking congenital predisposition to the condition, and in susceptible individuals the slightest injury may be followed by the formation of dense, often lobulated, fibrous tumours extending for some distance beyond the position of the original trauma. The nature of the irritant or injury, however, appears to be of some importance in determining the occurrence of keloid, and Unna quotes a remarkable case where it followed tattooing with red dye, though not with blue.

Not only is there a personal predisposition to keloid, but the racial incidence is also marked, and there is said to be a peculiar liability to it among negroes.

Although it has been claimed that the process may, in some cases, occur spontaneously, yet the amount of injury necessary to initiate it

has been proved to be so slight that every instance must, in all probability, be regarded as reactive in nature.

After removal the tumours recur since the process is repeated in the operation scar.

Microscopically, a keloid consists of dense bundles of swollen acidophil collagen, often hyaline in appearance, between which lie a few compressed fibroblasts. In the early stages the tumour may be more cellular, and there is usually a certain amount of cellular reaction around the cutaneous blood vessels adjacent to the periphery of the growth. There is an absence of elastic fibrils. Extension apparently takes place around the blood vessels of the deeper layers of the skin, and the process seems to be of the nature of a perivascular fibrosis affecting only these vessels. There is no true encapsulation

LIPOMA

Lipomata are slowly growing innocent tumours composed of adipose tissue. They have been described as occurring in many situations, but are most frequently met with in subcutaneous tissue, especially of the back and shoulders, in relation to serous and synovial membranes, and in muscles. More rarely, they may grow in the submucous coats of the alimentary canal and the larynx, in the periosteum of long bones, in solid organs such as the liver and the uterus, and in the meninges of the brain and spinal cord.

While the vast majority of these tumours arise from pre-existing fat cells, this is not invariably so, and they are occasionally found in parts which normally are entirely devoid of fat. In these cases we must suppose their origin to be from fat cells which have "wandered" in the course of the development of the body, "rests," in fact; or, with greater probability, ascribe them to a process of metaplasia occurring in fibromata.

Lipomata vary very greatly in size, some being many pounds in weight. They are usually single, and, although simple spheroidal forms do occur, the majority present a marked lobulation They are of a somewhat paler colour than the surrounding fat, and are always sharply encapsuled, being covered with a delicate coat of fibrous tissue from which rather coarser septa pass inwards between the lobules. Their true tumorous nature is well shown in starvation when a patient may be extremely emaciated and yet possess a pound or more unavailable fat locked up in a *lipoma*.

... lipoma is composed of fat cells of the adult type, ... tissue. Groups

of cells are separated by delicate strands of connective tissue, and the tumour is nourished by well-formed blood vessels surrounded by a fairly abundant fibrous tissue sheath (Fig. 15).

Occasionally the cells of a tumour approximate more closely to the fœtal type of fat cell, and contain several small globules of fat scattered through the cytoplasm, instead of a single large one occupying the whole of the cell. It is in the more rapidly growing lipomata that this condition is seen.

Although lipomata are typically innocent tumours, they may assume

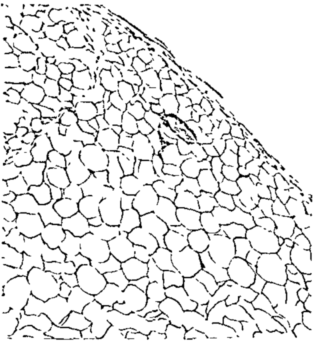

Fig. 15 Lipoma of the breast
Obj 16 mm apochrom Comp. oc. 6. Tube length, 160 mm.

malignant characters, when the fat cells are replaced by areas of rapidly growing sarcomatous tissue.

Fat enters into the composition of a variety of mixed tumours, giving rise to fibrolipomata (Fig 16), neurolipomata, myxolipomata, and angeiolipomata, and it is a common constituent of teratomata.

Apart from these mixed or compound neoplasms, the composition of lipomata is subject to alterations as the result of degenerative changes. The deposition of calcium salts may give rise to a dense, hard tumour, or softening may ensue from a diffuse mucoid degeneration of the cells Occasionally, liquefaction may take place with the production of cysts filled with oily fluid.

As in the case of fibrous tissue, a localised blastomatoid overgrowth of fatty tissue, quite distinct from the subcutaneous and abdominal deposits of the obese, is not at all uncommon. It is particularly well seen in the "diffuse lipoma" of the neck and in the massive "perirenal lipoma."

XANTHOMA

Xanthomata are tumours composed of modified reticulum cells containing a cholesterol-lipid mixture. They are not uncommon in the subcutaneous tissues but may be found in connective tissue throughout the body. In many cases they are blastomatoid conditions associated

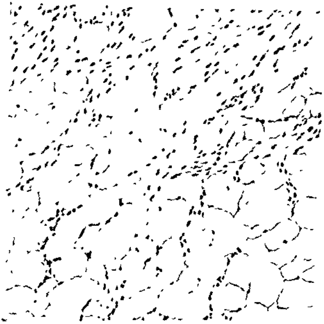

FIG. 16. Fibrolipoma of the intestine.
Obj. 16 mm. apochrom. Comp. oc. 6. Tube length 160 mm.

with a disordered lipoid metabolism and are *found* in diabetes, the Hand-Schuller-Christian syndrome and Niemann-Pick's disease, but it is probable that certain examples are true tumours; the subject has been well discussed by Thannhauser and Mangendantz[1] and Goldsmith.[2]

The tumours of the subcutaneous tissues are seldom large, but in the internal organs such as the peritoneum the xanthomatosis may be massive. They are often multiple and sometimes symmetrical in distribution, frequently on the eyelids or pressure points; in some cases the condition is familial. They are bright yellow to yellowish brown in

[1] *Ann. of Int. Med.*, 1938, **11**, 1662.
[2] *Recent Advances in Dermatology*, London, 1936, p. 347.

colour, firm and circumscribed. They grow slowly, but are seldom clearly encapsulated.

Microscopically they consist of closely set polyhedral cells having a small basichromatic nucleus with an unusually large finely vacuolated or foamy cytoplasm in which the cytoplasmic threads take up a reticulate arrangement between the masses of lipoid material; frozen sections stained with Sudan IV or other fat stains show the cytoplasm to be filled with fatty material and examination with polarised light reveals that much of this is anisotropic (doubly refractile) indicative of cholesterin. There is a fine reticulin network between the individual cells, but in a pure xanthoma there is little collagen and they are relatively avascular. They are not truly encapsulated, but the collection of cells compresses the adjacent tissue giving the appearance of a capsule. Sometimes multinucleate giant cells having a similar cytoplasmic character are to be found and in other examples there is a considerable collagenous stroma. In addition to the fibro-xanthoma. collections of xanthoma cells may be found in other types of tumours such as the giant cell tumour of bone. The histochemical constitution of the xanthoma cells varies in different conditions, but is commonly a mixture of cholesterol, cholesterol ester and phospholipoids.

MYXOMA

Myxomata are tumours composed of embryonic connective tissue similar to that present in the umbilical cord. They are among the rarest of all neoplasms, and while it is, perhaps, unjustifiable to deny their existence entirely as is sometimes done, it must be acknowledged that almost all the so-called myxomata are, in reality, instances of myxomatous change in other forms of connective tissue growths. Fibromata, Lipomata, and Chondromata are all particularly liable to this change, and myxomatous tissue enters largely into the composition of many of the mixed tumours of the parotid gland and the kidney. Recognised authorities, however, have described pure myxomata as occurring in several situations, more especially in subcutaneous and subserous tissue, in muscle, in bones, and in the endocardium.

Such growths form rounded, lobulated, elastic tumours, which, on section, exude a glairy, mucinous fluid. They grow slowly and are encapsuled.

Microscopically (Fig. 17), they consist of connective tissue cells which are widely separated from one another and possess long branching processes. By the interlacing of these processes a delicate meshwork is formed, the spaces of which are filled with mucin. The blood vessels

are usually capacious, and are surrounded by a varying amount of fibrous tissue. Frequently the vascular sheath is infiltrated with a considerable number of leucocytes, a condition which makes one rather sceptical of the true neoplastic nature of the growth. This histology may be closely simulated by œdema occurring in a fibroma, or even in a mass of chronic inflammatory tissue, and failure to recognise this has led to a considerable degree of confusion, notably with respect to the "mucous polypi" of the nasal mucous membrane. These are in reality œdematous polyps, usually of inflammatory origin, and have nothing to do with true myxomata. A more complete

Fig. 17 Myxoma of the jaw
Obj. 4 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

histological examination will always make the diagnosis clear, for frozen sections of a myxoma become granular after treatment with acetic acid from precipitation of the mucin, and, in paraffin sections, mucin gives characteristic reactions with differential stains such as muci-carmine and thionin

It sometimes happens that myxomata *lose their innocent* characters and assume malignant properties, growing with much increased rapidity and infiltrating surrounding tissues. These changes are reflected in the microscopic str[illegible]cture; the cells lose their branching [illegible] in type, while the mucin [illegible]

is absent [illegible]

Bearing in mind the rarity of simple *myxomata*, and the fact that

myxomatous degeneration is a common phenomenon in sarcomata, it is difficult to be sure in these cases that the tumours were not, from the first, sarcomata presenting advanced degeneration. But after the most rigid examination there remain a few instances where the malignant transformation of a myxoma seems the more reasonable explanation to adopt.

CHONDROMA

Chondromata are innocent tumours composed of hyaline- or fibro-cartilage. They are definitely encapsuled and of slow growth, and if of any size, are distinctly lobulated. On section they are of a bluish-grey colour and are semi-translucent. They are avascular and receive their nourishment from the blood vessels of the capsule. The central areas of large lobules may exhibit fatty or myxomatous degeneration, and in the variety known as the ossifying enchondroma there is a tendency to calcareous infiltration or even true bone formation.

Microscopically, the cartilaginous structure of the tumour is well maintained, though the cells may vary considerably in size and number, being small and numerous at the periphery where growth takes place, and larger and scantier in the deeper parts.

Tumours composed, wholly or in part, of cartilage are fairly common and may be roughly divided into four classes : (*a*) those growing near the ends of long bones—the osteochondromata or exostoses ; (*b*) those growing in the substance of the small bones of the hands, feet or spine and about the ribs or sternum—the chondromyxomata or enchondromata ; (*c*) in situations where cartilage is normally present, such as the larynx and bronchi , (*d*) in organs where cartilage is absent, chiefly the ovaries and testicles and the salivary glands. In only a small proportion of these tumours, however, can we say with certainty that we are dealing with true chondromata. In the first place, we have to distinguish between true blastomas and cartilaginous hyperplasias, for blastomatoid growths occur in cartilage as in other tissues, and many of these tumours are examples of simple hyperplasias. In other cases, especially the cartilaginous tumours of the testicle or ovary, we are in reality dealing with mixed growths, or teratomas. In certain examples the cartilaginous element may dominate the picture, but a careful search will almost always reveal the presence of other varieties of tissues as constituent parts of the growth.

The majority of chondromata grow in connection with the epiphyseal junctions of the long bones. They are commonest in childhood or adolescence, and often show a predisposition to occur in several

members of the same family. When chondromata arise in situations where cartilage is normally wanting it seems impossible to exclude a process of metaplasia occurring in the connective tissue of the organ.

Apart from malignant teratomas and chondrosarcomata, cases have been recorded in which chondromata, though apparently entirely innocent in their histological structure, have given rise to metastases, an accepted sign of malignancy. Now, there is no reason why a graft from an innocent tumour should not take root in a distant part of the host, for homologous transplantation of even normal tissues may be successfully achieved in a fair proportion of attempts. It is the spontaneous separation of grafts and their transference to other situations which is so suggestive of malignancy, and is so difficult to understand in the case of an innocent tumour. By virtue of their dense, elastic consistency, chondromata are not unlikely to ulcerate into veins, and when this happens the dissemination by the blood stream of minute fragments of the growth, or the actively proliferating cells of the perichondrium, is quite within the bounds of possibility. But it is probable that in most of the instances of the dissemination of a chondroma the tumours were not simple blastomas, but teratomas. The classical example of such a tumour is the malignant chondroma of the testicle, described by Paget, in a patient who afterwards died with secondary deposits in the lung. A further examination by Kanthack and Pigg demonstrated the presence of carcinomatous elements in the tumour, and these authors believed it to be a carcinoma with cartilaginous metaplasia of the stroma. Finally, Nicholson proved it to be a teratoma by discovering in it derivatives of all three primary germinal layers. With this example before us we should regard with some suspicion the formation of metastases by a simple chondroma.

CHORDOMA

Chordomata are uncommon, originating in the remains of the notochordal tissue, and are usually situated at the base of the skull, in the neighbourhood of the spheno-occipital synchondrosis, in the naso-pharyngeal region, in the bodies of the vertebra or in the sacro-coccygeal region.

The majority of them appear to be malignant rather than innocent, but they grow slowly and rarely disseminate, though the cranial tumours, from their position, are always serious.

Histologically, they consist of solid alveoli or strands of epithelial cells separated by connective tissue which for the most part is delicate and cellular but may be thick and dense. In the more cellular areas

the cells are epithelial in type ; as they mature they become progressively vacuolated forming the physaliphorous cells. These chordoma or physaliphorous cells vary in size, but are characteristically large polygonal cells with eccentrically placed vacuolated nucleus and pale-staining, often vacuolated cytoplasm. The vacuolation is due to mucin which often appears in the interstitial tissue, sometimes in such amount that the physaliphorous cells appear to float in it. Some of the

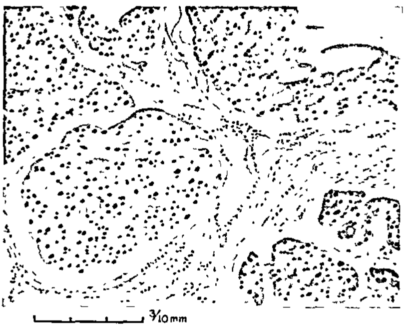

FIG 18. Section of a sacro-coccygeal chordoma, showing the alveolar structure of the tumour and the tendency to mucoid degeneration.

cross-sections of the strands may bear a fairly close resemblance to the embryonic notochord.

OSTEOMA

Pathological growth of bone is a common enough phenomenon both in connection with bony tissues and also in the soft parts, but we are very far from a complete understanding of its nature The technical difficulties associated with the histological examination of calcareous tissues are considerable, and possibly have been partly responsible for this state of affairs ; for we are content to employ such terms as "ossification," "exostosis," "calcareous degeneration," and the like, without troubling to attain to an accurate knowledge of the processes which have been at work

We may assert with some confidence, however, that only a very few osseous growths are blastomas ; the majority are inflammatory in

blastomas, growing progressively and causing destruction of the walls of the cavity.

A varying amount of bone may be found in slowly growing fibromata, but otherwise it is rare in innocent blastomas. It is, however, a fairly common constituent of teratomas, and frequently occurs in periosteal sarcomata.

ODONTOMA

This is an omnibus term used in a general way for any tumour-like mass developing from tissues concerned in the formation of teeth. They arise chiefly in young subjects and most often in the lower jaw

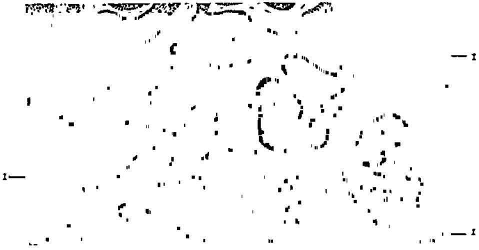

FIG 19 Microscopic section of an adamantinoma of the lower jaw. The tumour is composed of branching columns of epithelial cells lying in a fibrous stroma The inner cells of the columns are loosely packed together, and there is a tendency to the formation of cystic spaces (1).

Obj 16 mm apochrom Comp oc. 4 Tube length, 160 mm.

at the site of an unerupted tooth. The hard odontomata are nodular and consist largely of imperfectly formed teeth set in irregular masses *of enamel and dentine surrounded by a connective tissue stroma. The* soft odontomata are less common, they consist of connective tissue which is generally myxomatous and in it are rudimentary teeth and small islands of dentine There is no sharp division between odontomas and dentigenous cysts In these a cyst containing teeth is developed from the tooth follicle.

ADAMANTINOMA

A variety of odontoma formerly called **epithelial odontoma** and more recently adamantinoma arises from the enamel organ. The tumours are firm, usually contain small cysts and are often partly calcified.

Their microscopic picture is varied, typically they consist of solid strands and alveoli, composed of small undifferentiated epithelial cells in the centre and columnar cells in the periphery. Some of the alveoli may contain clear spaces or there may be cysts lined by columnar enameloblasts. The alveoli and strands are separated by varying amounts of well formed or young connective tissue. In some cases the epithelial cells resemble squamous epithelium. Adamantinomata have been described in the stalk of the pituitary and tumours resembling them are not very rare in this situation. If the stalk of the pituitary is carefully searched in about 50 per cent. of them small islands of squamous epithelium can be found. These are the remnants of Rathke's pouch. The adamantinomata arise from these islands, but whether they are in fact enamel organs is not so certain. Other "adamantinomata" have been described arising in the tibia, but in these cases it appears to be more likely that they are epithelial tumours than enamel organ tumours.

OSTEOCLASTOMA. GIANT-CELLED TUMOUR OF BONE

Osteoclastoma. Giant-celled Tumour of Bone. This is a locally malignant tumour occurring most commonly at the ends of long bones, being especially liable to attack the upper end of the tibia and the lower end of the femur. In the upper limb, the upper end of the humerus and the lower end of the radius appear to be the favourite sites. Besides the bones of the extremities, osteoclastomata may be found in the sternal end of the clavicle and the upper and lower jaws. They are rare in other situations.

Except for the myeloid epulis which grows from the periosteum, osteoclastomata take origin in the interior of bones. As osteoclastomata grow, the bone becomes expanded and absorbed, and a rounded tumour develops in the neighbourhood of the joint. The tumours do not infiltrate other tissues, but the bone is gradually absorbed, and may give way under slight pressure, with the production of the important clinical sign of "egg-shell crackling." Occasionally the bone may be entirely deficient over certain areas, and, since the tumours are highly vascular, pulsation may be perceptible at these points.

On section, osteoclastomata present a characteristic appearance. They are usually very hæmorrhagic and of a dark reddish colour (Fig. 20). As the result of old hæmorrhages and other secondary changes the colour may vary in different parts, and for the same reason

there is often extensive cyst formation (Fig. 21). Spicules of bone may be scattered through the tumour, and at the margin there is sometimes a zone of firm white growth.

The *microscopic* structure of the osteoclastomata is distinctive and

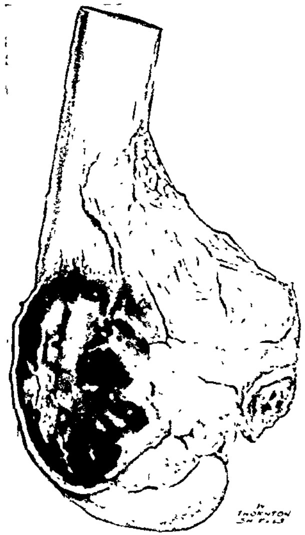

Fig. 22. Osteoclastoma of the lower end of the femur. The tumour is almost entirely hæmorrhagic, there being only a thin shell of solid growth at one periphery.

very curious when the relatively innocent nature of the growth is taken into consideration. It consists of a basis of round, oval and spindle indifferent cells of a decidedly sarcomatous appearance, and the giant cells which form the typical feature of the tumour. These are very numerous and variable in size, scattered somewhat irregularly throughout them are fairly large, oval nuclei which may, as shown in

the drawing (Fig. 22), be present in large numbers. The tumours are excessively vascular, being traversed by numerous delicate vessels, and they are consequently peculiarly liable to hæmorrhages. Evidence of old hæmorrhage in the form of phagocytosis of iron pigment is commonly found in the stroma.

During recent years a good deal of attention has been devoted to the pathology of these tumours. Whereas formerly they were

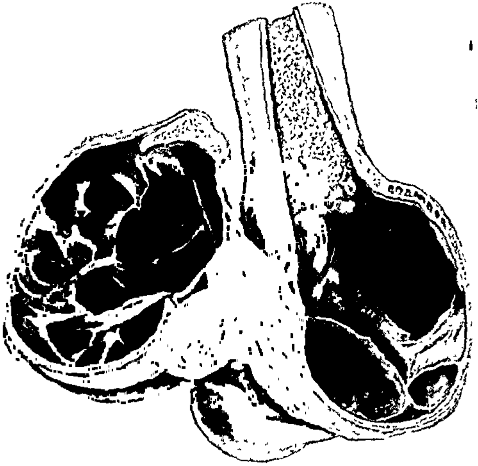

Fig. 21 Cystic osteoclastoma of the lower end of the femur

universally regarded as malignant and treated by amputation, it is now generally held that they are relatively benign and may safely be dealt with by thorough curettage or local excision. Stewart[1] holds that osteoclastoma is a true fibroblastic neoplasm arising in the fibrous reticulum of bone, and looks upon the typical giant cells as neoplastic osteoclasts Geschickter and Copeland[2] support this view.

[1] *Lancet*, 1922, ii, 1106
[2] "Tumours of Bone," New York, 1936

On the other hand, Jaffe[1] considers it to be a neoplasm arising from the undifferentiated connective tissue of the marrow and that the giant cell is not a homologue of the osteoclast and that if strict histological criteria are adopted the tumour is not so common nor so innocent as is commonly supposed. Bergstrand[2] suggests that the giant cells are not osteoclasts but osteocytes which have been unmasked as a result of a local bone resorption. He would trace a histogenic continuity between the traumatic hæmorrhagic bone cysts, the brown tumours observed in osteitis fibrosa generalisata and the giant-cell tumours or osteoclastomata.

These tumours are locally malignant and will recur unless treatment has been adequate, but they rarely disseminate. Inasmuch as true

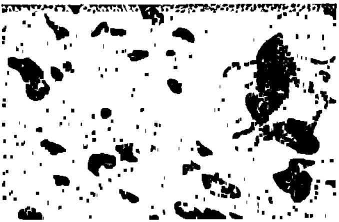

FIG. 22. Section of an osteoclastoma of the femur showing a vascular sarcomatous looking matrix and many multinucleated giant cells
Obj 8 mm, apochrom Comp oc. 4. Tube length, 160 mm.

osteogenic sarcomata occur in the same situation as the osteoclastoma, the differential diagnosis between the two is of great importance. In the true sarcoma the giant cells vary greatly in size and in the number and size of their nuclei. They may contain abnormal mitotic figures, and transition forms can be traced between them and the smaller cells of the tumour which themselves are often in process of division. In the osteoclastoma the giant cells are of the osteoclast type with regular nuclei; and neither they nor the smaller cells exhibit signs of unusual activity. There is, however, a possibility that an osteogenic sarcoma may arise at the site of a recurrent giant cell tumour. The myeloid-epulis and the giant cell tumour of the tendon sheath have a similar histology and natural history to those occurring in bone, though in

[1] *Arch. of Path*, 1940, **30**, 993
[2] *Am. J Canc*, 1936, **27**, 701

those arising in tendon sheaths xanthoma cells may also be present, when the tumours will be yellow.

LYMPHOMA

Lymphoid tissue is distributed very widely throughout the body, and readily undergoes hyperplasia *in response to irritation and infection*. Not only does the increase in size affect the established lymphatic glands, but *fresh nodes, often of a highly atypical structure*, make their appearance. Under these circumstances, it is easy to understand that the diagnosis of a lymphoma, *i.e.* a blastoma composed of lymphoid tissue, is a matter of some difficulty. Nevertheless examples of this form of innocent neoplasm have been recorded.

Of much greater interest are the blastomatoid conditions of lymphadenoid tissue, but there is great difficulty in distinguishing between a reactive hyperplasia, a progressive hyperplasia and a truly malignant neoplasm. In the lymphadenoid enlargements associated with tuberculosis and Hodgkin's disease we are on sure ground, for the histological changes are well recognised; but there are a number of less clear-cut conditions of varying histological appearance which are only beginning to be understood.

In contrast to hyperplastic and neoplastic conditions arising in most *other situations, there is a tendency for the conditions to affect lymphoid tissue* wherever it occurs and this multicentric form of proliferation is liable to be misinterpreted as embolic deposits from a *localised primary growth*. For example, in lymphoid leukosis (the tissue change commonly found in lymphatic leukæmia) there is a proliferation of lymphocyte-like cells *in the medullary portion* of lymphoid tissue throughout the body, in the periportal zones of the liver, the bone marrow, and on occasions the kidneys, *lung and dermis*; yet in typical cases there is no tissue destruction and the regular pattern of the cellular distribution is only explicable on the basis of multicentric autochthonous proliferation—a pathological process accepted in hyperplastic conditions of known ætiology such as the lymphoid reaction to the enteric group of organisms. However, the subject is one of great complexity and cannot be discussed in detail here.

MYOMA

New growths of muscle are divided into two classes according to their origin from smooth or striated muscle: they are named respectively, Leiomyomata, and Rhabdomyomata.

Leiomyomata, in their incidence, rank high among the innocent blastomas, though their distribution is somewhat restricted. They may grow in any of the situations where smooth muscle is found, for example, the skin, the wall of the alimentary canal, and the bladder; and they are quite common, though always of a minute size, beneath the capsule of the kidney. Except in rare instances, these tumours are small and of little practical importance. They grow slowly, are frequently multiple, and are invariably encapsuled. They seldom give rise to any symptoms, though in the alimentary canal, where they tend to become polypoid, they may exercise some mechanical interference with function.

But in one organ, the uterus, leiomyomata assume such notable proportions as to bring them into a class by themselves. The uterine "fibroids" are among the commonest of all innocent blastomas, and the most dangerous. They form tough, hard, spherical masses of a whitish or pale pink colour, and are sharply encapsuled. They originate in the substance of the uterine wall, and may always retain a covering of the normal muscle; but very frequently, as growth proceeds, they come to project above the external or internal surfaces, and are often pedunculated They are nearly always multiple, and may be very numerous, though the several tumours differ considerably in size. On section, their density becomes apparent, and the cut surface is smooth and often has a characteristic pattern made of whorled white fibres with smooth grey tissue between the fibres. The tumours themselves are not highly vascular, though there are, as a rule, many large vessels in their capsules.

[illegible] are composed of interlacing [illegible] ted with a varying amount [illegible] The two tissues are easily [illegible] the muscle taking a yellow colour with van Gieson's stain, and a much brighter pink with eosin than the fibrous tissue. The nuclei, too, are quite characteristic, those of the muscle being long with blunt ends, whereas the fibrous tissue nuclei are shorter and more sharply pointed. The vessels of the growth are well formed, and run in the fibrous tissue. In some tumours the fibrous tissue simply provides a scanty framework for the muscle fibres; but in others, especially the uterine myomata, it forms a considerable proportion of the whole tumour mass, and apparently grows equally with the muscular elements, so that the name "fibromyoma" is fully justified. Speaking generally, it may be stated that the larger the tumour is the more fibrous tissue it will contain.

Degenerative changes are not infrequent in myomata, and in the case of the important uterine fibroid they have been studied in some detail.

One of the commonest changes is an excessive proliferation of the fibrous tissue elements, leading to an increase in density and firmness of the tumour, and though this is scarcely a retrogressive change the process is usually known as "fibroid degeneration." The fibrous tissue is also affected in hyaline degeneration. Here the muscle fibres are untouched, but the fibrous tissue loses its structure and becomes

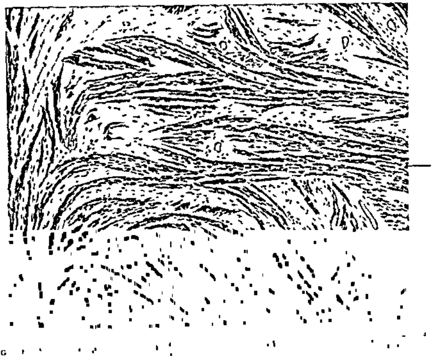

FIG [illegible]

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converted into a homogeneous mass of hyaline material. Myxomatous degeneration is fairly common, and here again the fibrous tissue is the one to be involved. This form of degeneration may be so extensive as to result in the production of large cysts filled with mucinous fluid. Fatty degeneration is fairly common, but is generally missed in the absence of frozen sections. Calcareous degeneration may be primary in a slowly growing tumour, or it may follow on a localised anæmic necrosis. It may be central or peripheral in its distribution. Necrobiosis, or red degeneration, appears to be due to the thrombosis of the capsular vessels, and is often associated with pregnancy. When it occurs the tumours become softer, and on section are of a deep red

colour. Septic infection with sloughing and necrosis may occur in the submucous variety of uterine myomata. Finally, it must be noted that simple atrophy of uterine myomata may take place after the menopause.

Leiomyomata are typically innocent tumours, and some authorities go so far as to assert that under no circumstances can they undergo a malignant change. This view, however, seems to be untenable. Fibroids of the uterus do undoubtedly become sarcomatous ; the point at issue is whether the change takes place in the muscular or the fibrous elements. It is not easy to furnish absolute evidence in either direction, but there is no reason why the muscle fibres should not give rise to sarcomas, and often the histological appearances strongly suggest that they do. In some cases of myosarcoma of stomach and intestines the appearances suggest that a sarcoma has arisen in a simple myomatous polyp.

Smooth muscle fibres rarely occur in mixed tumours, with the exception of the teratomata of the ovary and the testicle, where they are quite common.

Blastomatoid growths of smooth muscle are not of very great importance. Shattock has drawn attention to an overgrowth of the muscle fibres of the walls of arteries and veins in a fibroma, apparently blastomatoid in nature.

In the familiar senile hypertrophy of the prostate, again, there is usually a notable hyperplasia of the muscular elements of the gland.

Rhabdomyoma. Innocent tumours entirely composed of striated muscle are extremely rare, but they have been recorded as occurring in the heart, in the skeletal muscles (particularly in the tongue), in the uterus, the kidney, and the œsophagus.

It is doubtful whether mature striated muscle can ever give rise to tumours, and the generally accepted view is that rhabdomyomata always arise from fœtal rests, and those in the heart are most commonly found in children suffering from diffuse sclerosis of the brain and other congenital abnormalities.

The normal structure of striated muscle is never fully reproduced in such tumours, but the muscle cells are always irregular, both in size and shape, and frequently contain several nuclei. Further, cross striation is often absent altogether, or present only in parts of the fibre, and the cytoplasm becomes granular and acidophil.

Striated muscle, sometimes quite well formed, is occasionally found in mixed tumours, especially in the Wilm's tumour or embryoma of

the kidney, in the botryoid sarcoma of the uterus and in a few other cases of true rhabdomyosarcoma.

THE SARCOMATA

The sarcomata are malignant tumours derived from the connective tissues. They form a large and important class, and, on the whole, present problems of greater complexity to the histologist than do any of the other types of neoplasms.

They are essentially cytomata or cell tumours, and their elements never, except in the most rudimentary manner, combine so as to form distinct tissues. This is one of their most striking differences from the innocent connective tissue tumours, for these, as we have seen, are histiomata, and reproduce, although atypically, the structure of the tissues from which they arise. There are, no doubt, malignant representatives of each of the connective tissue histiomata, but their cells are so anaplastic in character that it is, often enough, impossible to determine their derivation.

Apart from the anaplastic nature of their cells, sarcomata possess in a high degree all the properties we have come to associate with malignancy: thus, they grow with great rapidity, infiltrate surrounding tissues, and give rise to widespread metastases.

In characteristic examples of either class we should have no difficulty in distinguishing between innocent and malignant connective tissue tumours. But it must not be forgotten that our classifications are, after all, purely arbitrary; there is always a zone where one order fades into the next. So it is with the sarcomata. Tumours of a comparatively slow growth and a certain degree of differentiation possess, to some extent, the characters of both innocent and malignant blastomas, and it may not be possible to decide in which class to place them

A further and more troublesome difficulty in the diagnosis of sarcomata is found in the likeness these tumours bear to processes of inflammation and repair. In both conditions the histological appearances may be similar, *e.g.* an undifferentiated type of cell, immature blood vessels, and an ill-defined margin of growth. In inflammatory conditions, of course, the type of cell is not, as a rule, uniform; but yet the resemblance between granulation tissue and some sarcomata is notorious.

An anomalous connective tissue reaction may also be seen occasionally in connection with carcinomatous growths. Very striking examples

of a highly malignant-looking proliferation of the stroma arise in epithelial growths of the breast, the gall-bladder, and the epiglottis, in which it is difficult to define the nature of the process.

It will be seen, therefore, that the study of sarcomata demands a considerable histological experience, and, even then, the diagnosis of individual cases may be purely a matter of opinion. Each observer has his own standards of what constitutes a sarcoma, and it seems quite probable that we must be prepared for a considerable readjustment of our ideas in the future, with the elimination of not a few of the conditions which we are now content to place in this group.

Nevertheless, in typical examples the histological features are sufficiently characteristic. The tumours are composed of actively growing undifferentiated cells, which are not closely applied to one another, but are surrounded by an intercellular matrix. In some tumours this matrix is more obvious and complete than in others, but in every case it can be demonstrated by appropriate methods of fixation and staining. At the same time, there is only a moderate amount of stroma, and the tumours are highly cellular. Occasionally, in the alveolar sarcomata, the stroma is more abundant, and broad bands of it may enclose solid masses of the tumour cells, so that the structure may bear some resemblance to that of a carcinoma. This formation, however, is rare, and the cells are usually scattered thickly and diffusely through the growth. It is to this absence of stroma that the peculiarly homogeneous naked-eye appearance so typical of the sarcomata is due, for there is no scaffolding to break the continuity of the tumour cells.

The nuclei of sarcoma cells show changes reflecting the vital activity of the tumours Mitoses, both typical and atypical, are numerous, while direct divisions and multiplication of the nuclei in single cells are not uncommon. Nuclear degenerations may be met with, but not so frequently as in the epithelial tumours, for it is more usual for the whole cell to die if the nutrition becomes imperfect.

The blood vessels of a sarcoma are ill-formed and consist of little more than a tube of endothelium. At the best they are invested by but a meagre sheath of connective tissue, and as a rule they course through the tumour in close contact with the cells which, in some cases even, themselves seem to line the vascular spaces This delicacy of the blood vessels is responsible for the hæmorrhage which so frequently takes place into the substance of the growth

The growth of sarcomata is peripheral and infiltrative, the tumour cells extending irregularly along fascial planes and lymphatic spaces

Metastatic deposits occur both by the blood stream and the lymphatics. From the intimate relation of the tumour cells to the vascular spaces, it is easy to understand the extension of the growth to the venous system: in most cases the spread is by embolism, but direct permeation of the larger veins is not unknown. Similarly, lymphatic spread takes place by permeation and embolism, and although this form of dissemination is obscured by the more obvious vascular one, invasion of lymphatic glands takes place quite often in these tumours.

As a natural consequence of the rapidity of their growth, and the extreme delicacy of their vessels, we usually find degenerative changes in sarcomata of any magnitude. Rupture of a vessel with extravasation of blood into the substance of the tumour is a very common happening, so much so that the probability of any excessively hæmorrhagic tumour being a sarcoma is generally recognised. As the result of this hæmorrhage, or possibly from thrombosis of some of the larger veins, considerable areas of the tumours may undergo quiet necrosis. A similar necrosis may follow in those tumours in which growth is so vigorous that the formation of new vessels fails to keep pace with it. A frequent change, though one often overlooked, is fatty degeneration. This is present in the majority of rapidly growing tumours, very many of the cells containing fat globules of varying sizes. Oedema and mucoid degeneration are common in fibrosarcomata, affecting chiefly the matrix; the tumours become soft and elastic, and large cysts filled with glairy fluid may be formed.

We have seen that it is not possible to adopt a purely histogenetic classification of sarcomata, however greatly this is to be desired, for as often as not it is impossible to determine from which variety of tissue the tumours are derived. In some cases, it is true, the tumour cells show a considerable degree of differentiation, so that we can readily recognise their nature; but in others the cells are undifferentiated and no recognisable tissue is formed. It is useful to divide sarcomata into these two classes, **differentiated** and **undifferentiated.** Among the undifferentiated we are accustomed to recognise the following varieties: small and large **round-celled sarcoma**, small and large **spindle-celled sarcoma**, and **polymorphic** and **giant-celled sarcoma.** These forms are to be regarded as the most malignant representatives of the connective tissue tumours, for in them anaplasia reaches its height, and their energies are directed entirely towards growth.

With a lower degree of anaplasia and a more fully differentiated cell, it becomes possible to adopt the more satisfactory histogenetic grouping, since in these cases we are able to distinguish malignant

neoplasms corresponding to the innocent **fibroma, lipoma, myxoma, chondroma, osteoma, lymphoma** and **myoma.**

These tumours occupy an intermediate position between the extremes of innocency and malignancy: it is often possible to trace in them the development of the anaplastic characters and a more extensive study of them may be expected to add materially to our knowledge of the derivation of the more malignant types.

Small Round-celled Sarcoma (Fig. 24). This is the most primitive type of blastoma and also the most malignant. It is composed of small

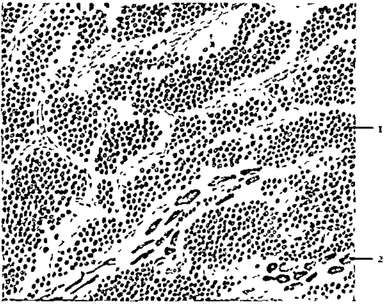

FIG 24 Small round-celled sarcoma infiltrating muscle (1) Sarcoma cells; (2) muscle fibres
Obj 8 mm apochrom Comp oc 6 Tube length, 160 mm

round cells, loosely applied to one another, and surrounded by the merest trace of a reticulated matrix. The cells resemble very closely the lymphocytes of the blood, but are slightly larger. They have a relatively large, round, deeply staining nucleus, sometimes situated eccentrically, which is surrounded by a scanty layer of cytoplasm. The tumours are highly vascular, being supplied by numerous delicate capillaries around which the cells are prone to collect. They exhibit retrograde changes to a marked degree. Hæmorrhages are almost invariably present, while many of the cells can be demonstrated to contain fat globules. It is also quite common for large areas of necrosis to occur in which the cells lose their staining reactions, and only a suggestion of the structure of the tumour can be made out.

Dissemination by the blood stream is widespread and rapid, and *generalisation of the growth* occurs very early; for this reason the tumours are practically always fatal in a few weeks or months. Local *infiltration along tissue spaces and fascial planes* is also extremely vigorous, so that operative treatment is of little use.

It is commonly believed that the small round-celled sarcoma is derived from the fibrous connective tissue of the body, but it is not unlikely that it represents the embryonic stage of all the tissues.

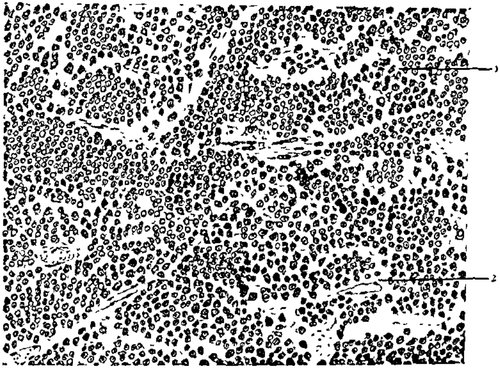

FIG. 25. *Large round-celled sarcoma of muscle.* (1) Sarcoma cells, some in process of division; (2) delicate stroma containing thin-walled capillaries.
Obj. 8 mm. apochrom. Comp. oc. 6. Tube length 160 mm.

Certainly there is nothing in its distribution to indicate its origin, for it may occur in any situation, though it seems particularly prone to arise in the fascia of muscles.

Large Round-celled Sarcoma (Fig. 25). The large round-celled sarcoma is also of wide distribution occurring in connection with muscle, skin, and many of the viscera. It is a highly malignant tumour, though it does not disseminate quite so rapidly or so widely as the small-celled form.

It differs from the small round-celled sarcoma in other important features. Its cells are larger, and possess much more cytoplasm. They are not always entirely spherical, but may be almost polygonal in

shape, and the nuclei are clearer and less dense. The matrix is still scanty, but shows a tendency to increase, and there is often a definite fibrous stroma which may be so marked as to result in the production of a distinctly alveolar structure.

In the viscera the large round-celled sarcoma occurs as a diffuse growth, but elsewhere, in as much as it has a certain degree of organisation of structure, it tends to form definite tumours of some size.

Degenerative changes are as common in this variety as in the small round-celled form, and are of a similar character. Dissemination takes

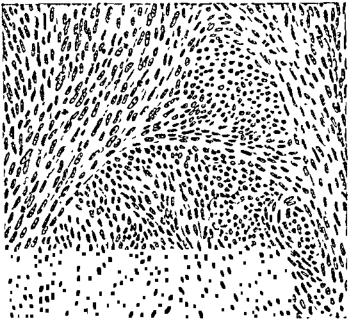

FIG. 26 Section of a spindle-celled sarcoma of the forearm
Obj 8 mm. apochrom. Comp oc 6 Tube length 160 mm.

place by means of the blood stream, and metastases are also usually present in the neighbouring lymph glands

Although it is true that there are connective tissue tumours so poorly differentiated that they can only be classified as small or large round-cell sarcomata, yet advances in histological technique have greatly limited their number.

Spindle-celled Sarcoma (Fig. 26). The majority of the more anaplastic sarcomata fall into this group, which, again, is subdivided according to the size of the constituent cells of the tumour. Such a subdivision, however, would appear to be of little practical value. It is purely arbitrary, for there is scarcely the same distinction between the small and large spindle-celled growths as there is in the case of the

round-celled sarcomas, and it affords us little or no indication as to the biological properties of the tumours.

The spindle-celled sarcomata occur in almost every tissue and organ of the body. The small-celled group are generally believed to arise from the fibrous connective tissues, while the larger-celled forms are more particularly associated with periosteum and smooth muscle.

The spindle-celled sarcomata are composed of fusiform cells, which vary a great deal both in length and breadth in different tumours; each cell contains a single long, oval nucleus, centrally situated. An occasional multinucleated or giant cell may sometimes be encountered, but these are rather rare in the pure spindle-celled sarcoma.

The cells are separated from one another by a fine homogeneous matrix, but are at the same time grouped together in bundles which lie in different planes, forming a close, interlacing feltwork. The structure becomes very evident in the microscopic section, for some of the fasciculi are cut transversely, others longitudinally, but it is too fine to be revealed to the naked eye. Not infrequently, fine strands of connective tissue may be scattered irregularly through the tumour, producing an imperfect, microscopic lobulation. Most of these tumours in which fibre can be identified are classified as cellular fibro-sarcomata.

The tumours are nourished by numerous capillary vessels which lie in close contact with their cells; so intimate is the relationship that the tumour cells seem sometimes to replace the vascular endothelium.

The spindle-celled sarcomata tend to form somewhat firm tumours, having a fairly sharply-defined margin, and often attaining a considerable size. Individual tumours vary in their rate of growth and in their power of forming metastases, but, as a rule, dissemination occurs later than in the types previously described. The common retrograde changes affect these tumours with some frequency, but while they are less liable to hæmorrhages than the round-celled forms, they very often exhibit advanced mucoid degeneration.

Polymorphic-celled Sarcoma. In its general characters this type of sarcoma does not differ greatly from the preceding group. Its cells, however, instead of being of a uniform type, exhibit an astounding variability in size and shape; and large and small, rounded and polygonal, oval and fusiform cells may all be present in the same microscopic field. Giant cells containing several nuclei are also frequent constituents of these tumours, indeed they may be the dominating feature, and it is owing to the occurrence of such giant-celled sarcomata that the confusion existed with respect to the osteoclastoma (giant-celled tumour) of bone.

Polymorphic-celled sarcomata are commonly found growing from bones, but they may occur elsewhere, and particularly striking examples have arisen in the breast and the uterus.

Turning now from the pure sarcomata to the intermediate forms, we have to deal with a less malignant, more highly differentiated neoplasm, in which it is possible to distinguish the nature of the constituent cell. All grades of cell differentiation are met with until a point is reached where it becomes impossible to state definitely that the tumour is really a sarcoma, possessing malignant properties.

FIG. 27. Section of a fibrosarcoma. The tumour is composed of large spindle cells, with occasional giant cells. There is much production of collagen.
Obj. 8 mm. apochrom. Comp. oc. 6. Tube length 160 mm.

It will be readily understood that the histology of these tumours exhibits great differences as we pass from the malignant to the more innocent types, and that there is room for a considerable divergence of opinion in the interpretation of their microscopical characters. Only by long experience can standards be acquired sufficiently just as to make an expression of opinion of value in difficult cases.

Fibrosarcoma (Fig. 27). The typical fibrosarcoma is a fairly firm tumour, having a comparatively slow but infiltrative growth. Only rarely, and then quite late, does it form metastases. It is more cellular than the innocent fibroma, and its cells are larger, more irregular in shape, and sometimes multinucleated; nevertheless, they tend to

produce fibres, and there is always more matrix than in the pure sarcomata.

Its vessels are unformed and are often quite large, and the tumours may become soft and cystic from œdema and mucoid degeneration.

With increased malignancy the general histology approaches that of the spindle-celled sarcomata.

So long as their malignant character is realised, it matters little whether we class the more anaplastic tumours among the pure sarcomata or the fibrosarcomata ; but at the other end of the scale it becomes necessary, and increasingly difficult, to distinguish between simple fibromata, fibrosarcomata, and those conditions of fibromatosis to which attention has already been drawn. Broders [1] has suggested a histological classification of the spindle-cell and fibrosarcomata in which the tumours are divided into four grades according to their degree of differentiation; he maintains that this is proportional to the prognosis.

Neurogenic Sarcoma. Many fibrosarcomas probably arise from nerve sheaths and are in reality neurogenic sarcomas. There is, however, no certain histological method of differentiating between a fibrosarcoma arising from fibrous tissue and one arising from the cells of the sheath of Schwann. Since no cells are exempt from tumour formation, such tumours will arise and some authors have demonstrated cells of sarcomas while still confined within epineurial sheaths. The frequency with which the diagnosis is made will, however, vary according to the bias of the examiner of the specimen. When the histological picture resembles that of a neurofibroma or a Schwannoma (*vide* p. 175), or if the tumour is in intimate relation with nerves it would be reasonable to call it a neurogenic sarcoma. When these features are not present it is impossible to distinguish eurogenic sarcoma from fibrosarcoma.

Liposarcoma. We have seen that all sarcomata ar prone to undergo fatty degeneration, and we must distinguish such tumours from the true blastomas derived from adipose tissue. Liposarcomata do exist, though they are undoubtedly rare. They may arise directly from fat cells, or may result from malignant transformation of the cells of a simple lipoma.

They are composed of cells of an embryonic type containing numerous small fat globules in their cytoplasm : these globules become dissolved out in the preparation of ordinary paraffin sections, when the protoplasm has a vacuolated, " foamy " appearance.

[1] *Surg. Gynec. and Obstet.*, 1939, 69, 267.

In the more malignant liposarcomata the cells revert to the undifferentiated, sarcomatous type, and only in the more mature parts of the tumour is it possible to determine their true character.[1]

Myxosarcoma (Fig. 28). In this class, again, we must distinguish between a retrograde process in a pure sarcoma and a true malignant blastoma of myxomatous tissue.

Myxomatous degeneration is common in the spindle-celled and fibrosarcomata, and the more slowly growing tumours may present large cysts filled with glairy, mucoid fluid The process seems to start in the intercellular matrix, which swells up and separates the tumour cells till eventually the structure becomes completely disorganised.

Fig 28 Section of a myxosarcoma of the thigh The cells are irregular in size and shape, and there is much formation of mucin A large thin walled capillary is situated in the upper part of the section

Obj 8 mm apochrom Comp oc 6 Tube length, 160 mm

The great majority of the so-called myxosarcomata come into this category, but, very rarely, malignant tumours are encountered whose cells have the power of secreting mucus These true myxosarcomata have a fairly high degree of malignancy, and form metastases with some readiness.

Chondrosarcoma (Fig. 29) The chondrosarcoma is derived from cartilage, and its cells retain, more or less imperfectly, the power of reproducing the structure of the parent tissue It occurs only in connection with bone or in those parts where cartilage is normally

[1] The liposarcomata have been well reviewed by Goormaghtigh, *Le Cancer*, 1936–37, **1**, 3, and Geschickter, *Am J Cancer*, 1934, **21**, 617

present; *in other situations cartilage forming* tumours are to be regarded as being teratomata.

The chondrosarcomata usually form rather massive tumours, and in their naked-eye appearances closely resemble *the innocent chondromata*; they are, however, much more liable to retrogressive changes, especially mucoid degeneration.

Microscopically, the structure varies with the degree of malignancy of the tumour. In the less active forms large lobules of unmistakable cartilage are produced, and the diagnosis can only be made by an examination of the growing margin. Here there is a zone of cellular,

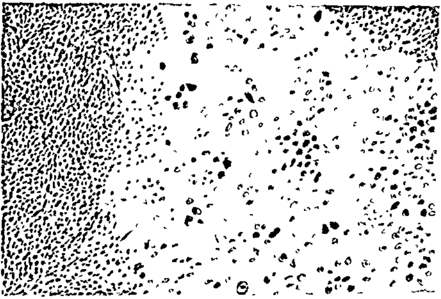

FIG. 29 Section of a chondrosarcoma of the larynx showing atypical cartilage with sarcomatous tissue at the periphery
Obj 16 mm apochrom. Comp oc 6 Tube length, 160 mm

distinctly sarcomatous-looking tissue, showing, in the number of mitotic figures present, evidence of rapid growth In the more malignant types the sarcomatous element predominates, and islands of imperfectly-formed cartilage occur only irregularly. Frequently, over considerable areas, there is no cartilage at all, only an excess of myxomatous matrix.

The chondrosarcomata do not as a rule grow with very great rapidity, and though they infiltrate and destroy the adjacent tissues, they do not usually disseminate at all widely.

Osteogenic Sarcoma (Fig 30). As its name implies, the osteogenic sarcoma tends to produce true bone; and, as we should expect from a consideration of the other tissue-forming sarcomata, all grades

may be met between the innocent osteoma, composed entirely of bone, and the fibro- or spindle-celled sarcoma, devoid of any recognisable tissue.

Macroscopically, the presence of bone-like material may be quite obvious, for it may form a great part of the tumour mass, but in other cases it may only be revealed by making thin sections through the whole substance of the growth. The presence of bony matter, however, does not prove the tumour to be an osteogenic sarcoma, for it may be simply the result of calcareous degeneration in a slow-growing fibro- or chondro-sarcoma. Again, a periosteal sarcoma sometimes erodes the surface of a bone irregularly so that small spicules become separated

FIG 30. Section of an osteogenic sarcoma showing the formation of spicules of bone (1) among the sarcomatous tissue (2)
Obj 8 mm apochrom Comp oc 4 Tube length, 160 mm.

and incorporated in the substance of the tumour, thus giving the impression of actual bone formation.

On the other hand, a tumour may form osteoid tissue consisting of trabeculæ, almost typical in every respect except that there is no deposition of calcium salts in the matrix; these of course will not be apparent on naked-eye examination.

The *microscopical* features of an osteogenic sarcoma are often most complex. The sarcomatous element is usually of the spindle-celled type, but the cells may be shorter and stouter, oat-shaped or even polymorphic. In the neighbourhood of the bone trabeculæ the cells are arranged as, and behave like, osteoblasts. Quite commonly the osteogenic sarcoma contains an appreciable admixture of cartilage, when the name osteochondrosarcoma is applied to the tumour.

It is convenient to divide the osteogenic sarcomata into sclerosing

and osteolytic varieties, the former are the typical osteosarcoma, whereas the osteolytic tumours are poorly differentiated polymorphic sarcomata with little tendency to form osteoid tissue and a tendency to osteoporosis of the surrounding normal bone.

The anaplastic types of this tumour grow rapidly and form metastases, but the bone-producing forms increase in size at only a moderate rate, and often remain entirely localised. The metastases may be pure sarcoma, or may themselves produce bone. The former is more usual, but cases have been described of an osteogenic sarcoma of the humerus, an enormous tumour which ulcerated extensively, where at the autopsy the only secondary growths were two small nodules in the infraclavicular glands of the same side, and one other nodule in the opposite lung, all of these consisted entirely of bone.

Reticulosarcoma. Reticulosarcoma is a generic term for a large variety of tumours derived from mesenchymal cells determined along hæmopoietic, lymphopoietic or histioid lines. The idea of a histogenic grouping is due to Oberling[1] and includes the lymphosarcomata, hæmic myelomata and certain tumours formerly classified as endotheliomata.

These tumours may arise in lymphoid tissue throughout the body including the lymphoid tissue of the pharynx and gastrointestinal tract, bone marrow and dermis, but can occur in almost any organ or tissue of the body. The majority of the tumours are radiosensitive, but their response to treatment varies according to the histological type.

Macroscopically they form large firm tumours with rounded irregular surfaces; on section they present a whitish homogeneous appearance broken by areas of hæmorrhage and degeneration.

The growth is infiltrative and metastasises readily to the regional lymph nodes with subsequent widespread dissemination by the blood stream.

A feature of the reticulosarcomata is the tendency to multicentric growth or systematisation; in some cases there is a definite primary mass with local lymph node involvement, but in addition neoplasms of similar histological character arise in lymphoid tissue throughout the body—a form of distribution inexplicable on the basis of embolic spread; in other cases there is no growth which can be regarded as primary, but neoplastic masses are found throughout the lymphoreticular tissue. In many of the tumours, particularly the lymphosarcomata, there is an associated leukæmia, and this may even be

[1] *Bull. Assoc franç. Cancer*, 1928, **17**, 259.

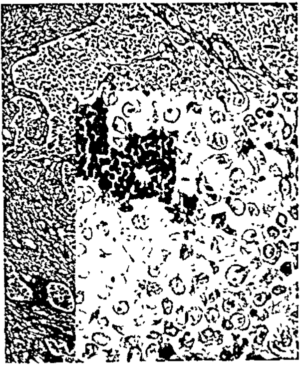

FIG 31 Secondary deposit of anaplastic carcinoma in a lymph node.

In the lower right hand corner is a high power view of the cells (× 300) showing the vesicular nuclei, poor in chromatin threads, while the cytoplasmic outline of the cells is sharp and there is a clear demarcation from the lymphoid tissue of the medulla

The rest of the photomicrograph is a low power view of a reticulin impregnation (× 70) showing the sharp demarcation of the infiltrating carcinoma cells from the reticulin stroma of the lymph node, and the malignant tissue is poor in reticulin fibrils

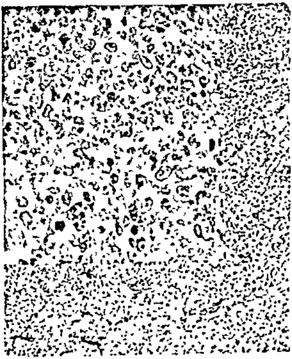

FIG 32 Syncytial reticulosarcoma

In the upper left hand corner is a high power view of the cells (× 300) showing the active mitoses, the synplasmic arrangement of the cells and the fine chromatin threads and prominent nucleoli of the reticulum cell nuclei

The rest of the photomicrograph is a low-power view of a reticulin impregnation (× 70) showing the almost complete absence of reticulin fibrils, apart from those in relation to blood vessels in this type of reticulosarcoma

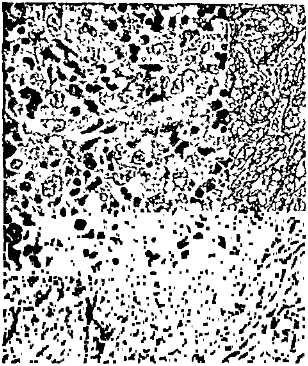

FIG 33. Dictyosyncytial reticulosarcoma

In the upper left hand corner is a high power view of the cells (× 300) showing the sheets of undifferentiated reticulum cells separated by polygonal or spindle-shaped cells with a chromatin-rich nucleus, some of which have a vacuolated cytoplasm (dictyocytes)

The rest of the photomicrograph is a low power view of a reticulin impregnation (× 70) showing the great increase of reticulin fibrils which are formed in relation to the dictyocytes and surround groups of reticulin cells

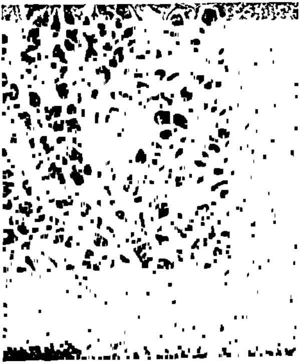

FIG 34 Dictyocytic reticulosarcoma

In the upper left hand corner is a high power view of the cells (× 300) showing the polygonal or spindle-shaped dictyocytes lying discreetly or in relation to fibres, the cells have an acidophil cytoplasm and a large pachychromatic nucleus with a large nucleolus

The rest of the photomicrograph is a low-power view of a reticulin impregnation (× 70) showing that the reticulin fibrils are in close relation to the neoplastic cells

found in cases in which the neoplastic process is localised and systematisation has not taken place.

Microscopically the reticulosarcomata have a variable structure according to their degree of determination and numerous classifications have been put forward,[1] but it is probably most convenient to consider them as undifferentiated, histioid and hæmic reticulosarcomata.

The undifferentiated or syncytial reticulosarcoma is composed of sheets of large pale-staining cells often arranged in a synplasma ; the nucleus is poor in chromatin , karyokinetic division is frequent. These

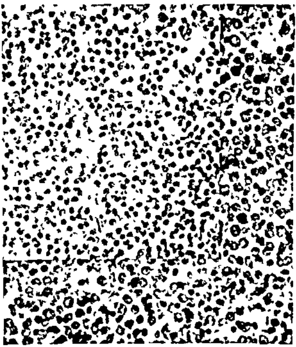

FIG. 35 Lymphoblastic and lymphocytic (lymphosarcoma) reticulosarcoma

In the upper left hand corner is a high power view of a lymphocytic reticulosarcoma, the rest of the photomicrograph is of a lymphoblastic reticulosarcoma at the same magnification (× 400)

In both the cells are discrete, but the lymphocytic cells are smaller, round with a very narrow rim of cytoplasm and a pachychromatic nucleus The lymphoblasts are commonly oval with a definite cytoplasmic edge, the nucleus has a well marked nuclear membrane and clearly defined nucleolus

tumours show no formation of fibrils but are rich in thin-walled capillaries (Fig 32)

These growths correspond to the condition previously described as endothelioma of lymph nodes, but there is no doubt that many of the tumours so described were in reality examples of secondary anaplastic carcinoma (Fig. 31)

In the histioid or dictyocytic reticulosarcoma the tumour cells form an intercellular network of reticulin fibrils The cells are discrete, polygonal with spurlike projections of the acidophil cytoplasm ; the nuclei are large, darkly staining with a prominent nucleolus and

[1] See Gery and Bablet, *Bull Assoc franç Cancer*, 1935, **24**, 615 ; De Oliviera, *Arch f path Anat*, 1936–37, **298**, 464 . Robb-Smith, *J. Path and Bact*, 1938, **47**, 457

mitotic division is infrequent. The **hæmic reticulosarcomata** are *formed of cells resembling those to be found in normal lymph nodes or bone marrow* and are the commonest forms of these tumours. The *cells of the* **lymphoblastic reticulosarcoma** are oval or round with a pale-staining nucleus which is sometimes indented and they lie in a *loose network of reticulin fibrils* and thin-walled capillaries.

In the **lymphocytic reticulosarcoma or lymphosarcoma**, the cells are *smaller, resembling* small lymphocytes of the blood with a narrow rim of cytoplasm surrounding a round darkly staining nucleus. The

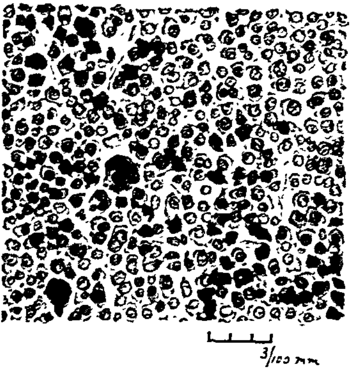

Fig. 36. Section of a plasma-celled myeloma of the radius.

growths are well supplied with capillaries and have a loose reticulin stroma which is said to be more abundant than in the small round-cell sarcoma (Fig. 35).

Multiple myelomatosis (hæmic myeloma or plasmacytoma) is the typical example of a hæmic reticulosarcoma arising in the bone marrow and owing to its tendency to stromal destruction and more rarely to embolic metastases must be regarded as malignant, though some pathologists consider it as a hyperplastic or blastomatoid condition more closely related to the leukoses.

In this condition grey or reddish tumours occur throughout the marrow cavities, but more particularly in the ribs, vertebræ and

cranium (the sites of red marrow in adult life). The tumours induce an osteolysis by attrition and curvature of the spine and spontaneous fractures may occur In some cases there is involvement of the lymph nodes, liver and spleen and dermis

The type cell in the majority of cases resembles the plasma cell or its precursor and Russell's acidophil inclusion bodies may be found; more rarely the predominant cell resembles an erythroblast or myelocyte and mixed forms have been described. The blood picture usually shows a hypochromic anæmia and neutrophil leucocytosis, but in a few cases a plasma cell leukæmia has been observed. Sternal puncture usually reveals an excess of plasma-like cells in the bone marrow It is common to find an increase in the plasma proteins chiefly in the globulin fraction and the sedimentation rate is very rapid; there may also be changes in the calcium and phosphorus consequent on the decalcification and renal failure. In a certain number of cases the Wassermann reaction is positive although there is no history or evidence of syphilis. Further evidence of disturbance in the protein metabolism in this condition is shown by the excretion in the urine of a curious albumose—Bence Jones Protein—which is precipitated between the temperatures of 50° and 60° C, and re-dissolves at a higher temperature; its exact chemical nature has not been determined though it may on occasion be found in crystalline form. Bence Jones protein is only found in about 50 per cent. of cases and may rarely be found in other diseases involving the bone marrow. The kidneys in many cases, even those without Bence Jones proteinuria show a severe tubular degeneration with interstitial fibrosis and another curious feature observed in certain cases is a widespread deposit of a substance resembling amyloid which is not laid down in the sites commonly found in amyloidosis associated with chronic sepsis, but around the joints and the muscular tissue of the intestinal tract, heart and tongue.

Multiple myelomatosis arises most frequently in the fifth and sixth decades and the duration of life is about two years, although radiation therapy gives symptomatic relief.

Cases of plasma-cell myeloma limited to a single bone have been described and cures claimed as the result of amputation; although there is no doubt that solitary plasmacytomata do arise either in bone or in the nasopharynx, yet in the majority of cases careful examination reveals evidence of systematisation and if this is not found at the time it usually develops.

Chloroma is a condition generally occurring in young people and is

characterised by the appearance of periosteal tumours in the skull, vertebræ, ribs and sternum. When examined in the fresh state these tumours present a greenish colour which rapidly fades on exposure to the air but can be restored by the application of strong reducing agents. The tumours are in the nature of an infiltration of the periosteum and muscles with cells resembling myeloblasts and are invariably associated with a myeloblastic leukosis although a leukæmia may not be found at first. There is seldom any bony destruction or proliferation and the nature of the green pigment is unknown; it is sometimes to be seen in the bone marrow in ordinary cases of myeloid leukosis and shows a brownish red fluorescence under ultra-violet light.

FIG. 37. Section of a leiomyosarcoma. The tumour is composed of bundles of smooth muscle fibres supported by a fibrous tissue stroma.
Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

Polymorphic reticulosarcoma is a mixed type tumour in which there is a proliferation of hæmic and histioid cells with atypical giant cells. Mitosis is frequent and there is an irregular increase in reticulin and collagen fibres; these tumours are vascular and necrosis is a common feature.

They correspond to one of the conditions often known as Hodgkin's sarcoma or malignant Hodgkin's disease and frequently arise in the intestinal tract whereas lymphadenoma verum is seldom found in this situation.

Leiomyosarcoma (Fig. 37). It is not often possible to be sure that a sarcoma is derived from smooth muscle, though it is quite likely that many spindle-celled sarcomata are muscular in origin. But occasionally one meets with a tumour which, though it shows no naked-eye

peculiarities, can be diagnosed with certainty from its microscopical characters as a malignant growth of smooth muscle.

The distinguishing features of such tumours are the nuclei and the arrangement of the cells.

The nuclei may be numerous, but are often scanty as compared with the ordinary spindle-celled sarcoma; they are longer than usual, and have blunt or rounded ends; mitotic figures are often present.

FIG 38 Section of a rhabdomyosarcoma showing the irregularity of the tumour cells with imperfect cross striation.

The cells are arranged in bundles as in the spindle-celled sarcoma, but they do not interlace so closely, being separated by a distinct connective tissue stroma in which run the nutrient vessels. Often it is possible to make out a longitudinal striation in the cells, but this is not invariable.

The leiomyosarcomata are highly malignant tumours, forming metastases in lymph glands and in the viscera.

Rhabdomyosarcoma. Pure malignant growths of striated muscle are

rare, though they are occasionally found in the genito-urinary tract, pharynx, and elsewhere: teratomata containing striated muscle fibres are more common.

Macroscopically these tumours often show a characteristic appearance when projecting from mucous membranes. They then have a lobulated polypoid structure with translucent clubbed processes, coarser in form than adenomatous polypi.

The histology of these tumours is very variable (Fig. 38). They are composed for the most part of large irregular cells, often possessing long, broad processes, and surrounded by a fairly abundant intercellular substance. Giant cells are not uncommon.

To establish the diagnosis it is necessary to demonstrate cross striation in the cytoplasm, and this may be extremely difficult to do. *It may be present in the processes or in the body of the cell, or it may be absent altogether*

Cappell and Montgomery[1] have suggested that the term myoblastoma should be reserved for neoplasms whose cells morphologically resemble muscle cells, but which are devoid of transverse striation. The myoblasts have a strongly acidophil, often granular, cytoplasm and are spindle shaped or *may have one broad end and the other short and* narrow. In some tumours they form a pavement of polygonal or oblong closely packed cells They are often multinucleate and the nucleus is oval and vesicular with single prominent nucleolus Occasionally these cells show a tendency to longitudinal striation, or at any rate a linear orientation of the cytoplasmic granules.

THE INNOCENT EPITHELIAL TUMOURS: PAPILLOMA AND ADENOMA

Before entering upon a description of the epithelial tumours, it is necessary clearly to understand the nature of the tissue with which we have to deal.

The epithelial cells form the lining membranes of the surfaces of the body, and certain *solid glandular structures derived from them;* they therefore possess the features to which Adami has directed attention as being peculiar to all lepidic tissues. Whatever their arrangement may be, whether spread out as a covering to a surface, or collected together as a solid organ, epithelial cells are always in absolute contact with one another, *there is no intercellular substance*

[1] *J Path. and Bact*, 1937, 44, 517.

such as we have seen is universally present in all hylic or connective tissues.

The collections of cells are supported by a scaffolding or stroma of connective tissue which renders it possible for any particular epithelium to assume its distinctive arrangement.

Not only does the connective tissue support the epithelium, but it is of vital importance to its nutrition, for all the blood and lymphatic vessels are contained in the stroma, are, in fact, integral parts of it.

It is obvious, then, that epithelium cannot exist apart from connective tissue, and further, that the growth of the stroma must keep pace with that of the epithelium.

It is in view of this intimate relationship that benign neoplasms of epithelium have been described by some authors as **fibro-epithelial** tumours. Such a title, however, does not seem to have much real justification for its use, for it does not express the essential nature of the tumours, but rather creates confusion. After all, the proliferation of the epithelium is the thing that matters; the accompanying growth of fibrous tissue is purely subservient to it. It is not denied that combined epithelial and connective tissue tumours do occur, tumours in which both elements progress equally, but they are rare; a more careful examination almost always enables us to distinguish one or other element as the predominant partner.

The innocent epithelial tumours are histiomata; that is to say, they reproduce, although atypically, the structure of epithelial tissue. According to the mode of growth, therefore, two main types exist—the papilloma corresponding to the surface or covering cells, and the adenoma corresponding to those of the secretory or glandular organs. When a papilloma arises from a glandular surface it is a papillary adenoma

In the papilloma the cells are situated externally, being arranged around an internal core of connective tissue; in the adenoma they form tubules or solid masses, which are embedded in, and surrounded by, the connective tissue stroma.

In the latter group it is not uncommon for the tubules to dilate into cysts of varying size, and for the lining epithelium to project into the cavity in a papillomatous manner, giving rise to a **papillary cyst-adenoma.**

Although they exhibit differences in growth and behaviour depending upon their individual structure, papillomata and adenomata agree in their general properties, and these may be conveniently discussed now.

In the first place, these tumours are innocent: they progress

[illegible] the difficulties attendant on [illegible] malignant growth, [illegible] which seem to prove [illegible] illustrate suc[illegible]

Befo[illegible]
necessary [illegible]
have to d[illegible]

The epith[illegible]
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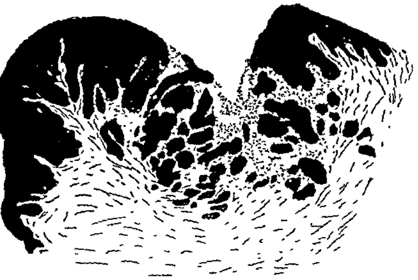

FIG. 43 Malignant papilloma of the tongue Compare with Figs 41 and 42. The overgrowth of the superficial epithelium is not so marked, but columns of epithelial cells are passing downwards among the deeper tissues Semi-diagrammatic, × circ 16

FIG 44 Section of a villous papilloma of the bladder (1) Papilla cut longitudinally, showing connective tissue core with covering of stratified epithelium, (2) papilla cut transversely, showing central blood vessel in connective tissue core

Obj. 16 mm apochrom Comp. oc 4 Tube length. 160 mm

(*b*) **The mucous or soft papilloma** presents a distinctly villous appearance. It is composed of long delicate processes attached around a somewhat slender central stalk (Fig. 44). Such tumours are found mainly in the alimentary canal, especially the lower bowel, and in the urinary bladder, though they may, of course, occur in many other parts of the body. In the bladder they are extremely soft and bear quite a striking likeness to certain seaweeds, and they frequently involve large areas of the mucosa.

Another type of soft papilloma, characteristically seen in the intestine, consists of a solitary thick finger-like process, hundreds of

FIG. 45 Pseudomucinous cystadenoma of the ovary The tumour contains large cystic spaces, lined with columnar epithelium, and filled with mucoid fluid and cell debris From the lining epithelium numerous papillomatous ingrowths project into the cavities of the cyst.

Obj 16 mm. apochrom Comp. oc 4 Tube length, 160 mm

which may be present in the condition known as adenomatosis of the colon. In certain cases this polyposis is inherited and these patients show an extremely high incidence of carcinoma of the colon.

A soft papilloma, intermediate in structure between the above, forms the commonest tumour of the larynx, and may also occur on the tongue.

(*c*) **The intracystic papilloma** (Figs. 45 and 46) may consist of a coarse branching growth, or it may more approach the villous type. It is seen to perfection in cystic ovarian tumours and in cysts of the breast.

Microscopically the simple papilloma is composed of a layer of cells covering a core of vascularised connective tissue. At its inception the

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Microscopically the simple papilloma is composed of a layer of cells covering a core of vascularised connective tissue. At its inception the

tumour consists simply of a budding or folding of the superficial epithelium, the two layers of ingrowing cells being separated merely by the basement membrane which accompanies them. As growth proceeds, fibrous tissue and capillary blood vessels insinuate themselves

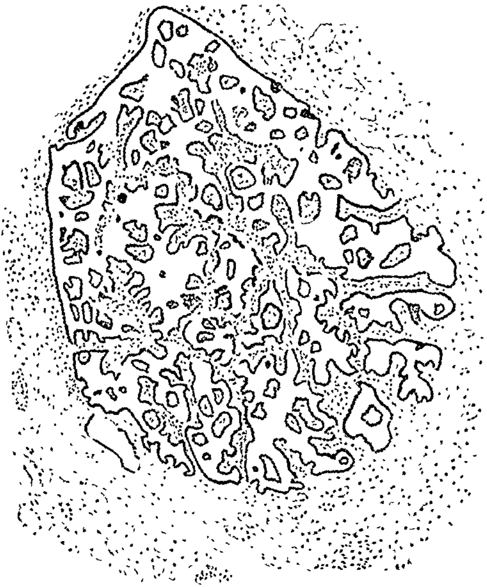

Fig. 46. Papillary adenoma of the kidney.
Obj. 16 mm apochrom. Comp. oc 4 Tube length 160 mm

between the layers of the basement membrane, and the structure becomes complete. Secondary outgrowths of the epithelium and stroma will give rise to the more complex compound papillomata. In the majority of cases the cells are several layers thick; and though they are usually well formed and typical, this is not always so, and

they may differ widely from their normal prototypes. In the intracystic papilloma there is often only one layer of cells. The squamous papilloma shows a considerable variation in structure. It may conform to the typical arrangement, or it may largely consist of a simple heaping up of the epithelium with a very imperfect formation of stroma.

The rectal papillomata have usually a complex adenomatous

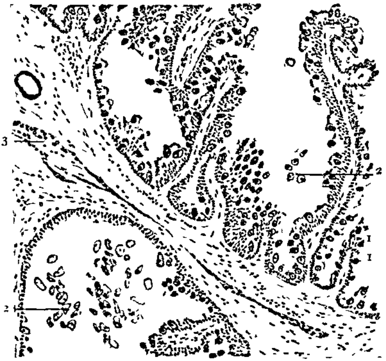

FIG 47 Coccidiosis of the rabbit's liver There is extreme cystic dilatation of the bile ducts with papillomatous ingrowth of the lining membrane Numerous coccidia can be seen in the epithelial cells (1), and some are lying free in the cysts (2) compressed liver cells (3)

Obj 8 mm apochrom Comp oc 4 Tube length, 160 mm

structure, the form and arrangement of the glands being very like that seen in the normal mucous membrane.

The striking similarity which exists between blastomatoid conditions and true blastomata is very clearly shown in the papillomata, for the more we study these tumours, the more obvious does it become that the majority of them are really hyperplastic and reactive processes. In some cases it is a known infection which gives rise to the papillomatous proliferation of the affected cells; in others we can with safety deduce an infection from the clinical aspect of the lesion, though the

causal agent remains unknown. Or, as in the case of the worker in paraffin, an obvious source of chronic irritation may have been present for a considerable time.

The most striking examples of parasitic papillomata are seen in Coccidiosis of the rabbit and Bilharziasis of man. In the former disease the animal's liver is studded with round whitish tumours which, upon examination, are found to consist of proliferated bile ducts. The tumours have the structure of papillary cystadenomata, but the existing agents, the coccidia, are present in great numbers in the epithelial cells and in the cysts themselves (Fig. 47). In man, the presence of the ova of the bilharzia in the rectum and the bladder gives rise to a papillomatous hyperplasia of the mucosa scarcely to be distinguished from a true blastoma; moreover, this condition may gradually become carcinomatous.

With regard to the skin, an analysis of the various forms of papilloma which occur suggests that an authentic blastoma of this type is a rarity. To quote a few of the more striking examples, the multiple warts of childhood are infective in nature, caused by a virus; and the same may be said of the venereal warts which form massive papillomata on, and in the neighbourhood of, the genital organs, usually in association with a chronic gonorrhœa. Again, molluscum contagiosum is an infective disease due to a filter passing agent and elementary bodies are present in very large numbers in the cytoplasmic inclusions or molluscum bodies. It is characterised by the formation of small umbilicated warts on the skin, especially of the face and head. The histology is distinctive, consisting of a papillomatous overgrowth of the cells of the surface epithelium with a peculiar hyaline degeneration of those of the deeper layers.

Adenoma

The adenomata are innocent tumours, having a slow rate of growth and a sharply-defined margin

They are composed of epithelial cells which in their size, shape, and general regularity of form approximate very nearly to the normal, and these are arranged in such a manner as to reproduce with a considerable degree of accuracy the structure of the tissues from which they are derived.

Since all the different glandular tissues of the body may be the seat of neoplastic processes, it follows that the adenomata present a very varied structure. It is, however, unnecessary to enter into a detailed description of all the types, and we may content ourselves with a

consideration of those characters which are common to these tumours as a whole.

The site of origin influences to some extent the mode of growth of the tumours, and enables us to divide them roughly into two classes, the intraglandular and the polypoid. Thus, the adenomata arising in the substance of a glandular organ are more or less spherical in form and are sharply encapsuled; if, however, they grow in a mucous membrane such as that lining the alimentary canal or the uterus, their shape is somewhat more irregular, and they are nearly always pedunculated.

Again, the structure of the tumour is largely dependent on that of the parent organ. For example, in solid glands such as the liver, the adrenal gland, and the sebaceous glands of the skin, the cells of the tumour will be massed together in trabeculæ or solid acini, with little or no attempt at the formation of alveoli; but in adenomata of tubular or racemose glands, a tubular or alveolar arrangement is the rule. This distinction, however, does not always obtain, for alveoli may be found in tumours of the former group, and in the latter there may be a solid acinor structure.

Of greater importance is the high degree of differentiation possessed by the cells of adenomata. In the majority of cases they are capable of carrying on their normal functions to a considerable extent, and so we find bile produced in adenomata of the liver, "colloid" in the tumours of the thyroid, and mucin from the goblet cells of the intestinal growths Where the secretion of mucin or colloid is abundant, the structure of the tumour will be proportionately modified, for the arrangement of the alveoli is quite irregular, and there is no provision for the removal of the secreted material such as is provided by the ducts of the normal gland. The alveoli will become distended with the retained secretion, with the result that the tumour is converted into a collection of cysts, a cystadenoma.

The cells lining the cysts may gradually atrophy from pressure of the contained fluid, or they may remain active and grow into the lumen, giving rise to the papillary cystadenomata with which we are familiar in connection with the breast, the thyroid, and the ovary.

In the tubular adenomata (Figs. 48 and 49) the cells naturally vary in shape in different tumours; in some they are of the high columnar type, in others low or cubical. They are usually arranged in a single layer which rests upon a basement membrane composed of condensed connective tissue, but quite commonly they may be two or three layers deep In spite of statements to the contrary, it is important to realise

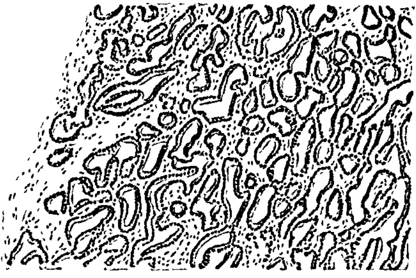

FIG. 48 Tubular adenoma of the kidney The tumour consists of irregular elongated tubules lined by a single layer of epithelial cells

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FIG 49. Adenoma of the breast The epithelial tubules are irregular in shape, and are often lined by two or more layers of epithelial cells. The stroma is dense and abundant

Obj 16 mm, apochrom, Comp oc 4 Tube length, 160 mm

that such a multiplicity of cells lining the tube is not necessarily a sign of malignancy, but is quite a common feature in innocent tumours.

Reference has already been made to compound epithelial and connective tissue tumours, in which both tissues play an equally important part. The most characteristic examples of this group are

to be found in the fibro-adenomata of the breast, where, associated with a hyperplasia of the glandular elements, there is a progressive growth of the fibrous tissue. Two main types exist. In the first, the **pericanalicular fibro-adenoma** (Fig 50), the fibrous tissue growth is chiefly marked around the gland acini which themselves show a pronounced hyperplasia. In the second, the **intracanalicular fibro-adenoma** (Fig. 51), the fibrous tissue grows in an irregular manner so that the tubules become stretched round it in such a way that the

FIG 50 Pericanalicular fibro-adenoma of the breast The breast acini (1) show little change but the fibrous tissue is increased in amount and is highly cellular, it forms a particularly dense sheath around the acini (2)

Obj 15 mm apochrom. Comp oc. 4 Tube length, 160 mm

fibrous tissue appears to be within the tubules. There is a tendency to the formation of cysts which become occupied by projections or ingrowths of the fibro-adenomatous tissue.

Only rarely do these tumours seem to be in reality compound growths, usually either the fibrous tissue or the epithelium is the seat of the original progressive change, and in the majority of cases it is the fibrous tissue, so that it would be more correct to describe them as adenofibromata

Progressive overgrowths of epithelium of a blastomatoid nature are numerous and difficult to distinguish from true blastomas Some are

apparently the result of some form of chronic irritation, in others the cause is more obscure. In the liver and the thyroid gland it is almost impossible in many cases to differentiate between simple regenerative processes, reactive hyperplasias, and blastomas; and similar difficulties are met with in respect to the breast and the prostate. While it is unnecessary to labour the point, or to multiply examples, it must be

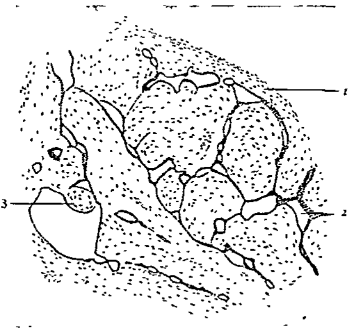

FIG 51 Intracanalicular fibro-adenoma of the breast. There is a diffuse hyperplasia of the fibrous tissue (1), and the acini are elongated and distorted (2), the fibrous tissue is not within the lumen but distorts the tube (3)

Obj 16 mm, apochrom. Comp. oc. 4. Tube length, 160 mm.

remembered that the nature of a "tumour" composed of epithelial cells may be quite as obscure as a similar growth in the connective tissues.

THE CARCINOMATA

In many respects this group is the most important of all those we have to study. It is important numerically, for a considerable proportion of all the neoplasms of any clinical significance belong to it, and its members, by virtue of their distinctive structure, afford unrivalled facilities for the general study of the origin, growth, and spread of tumours.

The carcinomata are malignant epithelial tumours, bearing the same relationship to the innocent epithelial tumours as do the sarcomata to the innocent connective tissue growths.

They are, therefore, cytomata, and are composed essentially of epithelial cells which are not arranged so as to form tissues.

But, as in the sarcomata, malignant tumours occur in which we can distinguish the formation of an atypical issue, so in the carcinomata the cells may be grouped together to form a recognisable lining epithelium or gland tubules. Occasionally the resemblance to the normal tissue is so close that there may be considerable difficulty even in deciding whether a given tumour should be classed among the adenomata or the carcinomata, and this not only in those intermediate or borderline tumours which, naturally, we should be prepared to meet with from time to time, but also in growths having a very definite degree of malignancy.

Nevertheless, the rule holds good in the majority of cases, and whereas the adenomata mimic with some exactitude the tissue from which they are derived, though the structure of the organ is not reproduced, the carcinomata are composed of epithelial cells which rarely form more than the imperfect rudiments of a tissue.

Although in the majority of carcinomata the cells of the tumour are obviously of the epithelial type, this is not always so, and it is necessary to keep in mind the fact that anaplasia is one of the most striking characteristics of the malignant cell. The more malignant a tumour is, the more will its elements deviate from the normal and its cells fail to mature; and although the cells certainly retain their lepidic characters in being in absolute apposition with one another, it is only by the study of a series of tumours of varying malignancy that we can trace the connection between normal lining or glandular epithelium and the more undifferentiated carcinomata.

The naked-eye appearances of the carcinomata are extremely variable. It is usual to describe three main forms, the ulcerative, the nodular, and the fungating; but in the finer details no two tumours are exactly alike, and even the grosser features depend very largely upon factors of quite secondary importance.

The colour is usually white or grey, and the consistence is harder than that of the surrounding tissues.

The cut surface is nearly always granular, a mat surface which may be mottled yellow or red from fatty degeneration or hæmorrhage, while mucoid degeneration will give a translucent " colloid " appearance.

The presence of a stroma makes the carcinomata seem to have a more organised structure than the sarcomata, and helps considerably in the differential diagnosis between the two growths.

Much of what it is necessary to say concerning the general properties

of the carcinomata, their origin, growth, and dissemination, will be found in preceding chapters; we need consider now only some of their more particular features.

The structure of a carcinoma is very much more complicated than that of a sarcoma, for it consists not only of the essential epithelial cells of the growth, but also of the blood vessels and connective tissues which nourish and support them. And though the connective tissue element appears to be of secondary importance, it plays a very necessary part in the life of the tumour. If, from one cause or another, the blood supply is inadequate, the tumour cells will die; if, as may sometimes be seen in small malignant emboli in blood vessels, the connective tissues fail to supply a supporting scaffolding, the cells are unable to survive, or if the connective tissue reaction is excessive, the parenchymatous elements may be partly or entirely choked and killed.

It is not out of place, therefore, to enquire a little more closely than we have hitherto done into the nature and origin of this stroma.

A carcinoma may increase in bulk in two ways: it may infiltrate the surrounding healthy tissues, destroying the specific cells of the part and utilising as a stroma the existing connective tissues; or it may exhibit a combined growth of its cells and stroma, quite apart from any addition to its mass by the absorption of surrounding structures.

While the former mode of progression is characteristic of the carcinomata, as it is of all malignant growths, and is of much greater clinical importance, it is easy to demonstrate that both are active simultaneously, though not necessarily to the same extent.

If we examine secondary carcinomatous nodules in an organ such as the liver, we are struck by the fact that the superficial metastases project only slightly above the surface, though they extend for some distance into the substance of the organ. In other words, the growth of the tumour is mainly at the expense of the pre-existing tissues.

Nevertheless, there is a certain amount of independent growth on the part of the tumours, for they often are raised to some extent above the surface, and their deeper margins are fairly sharply defined; moreover, a microscopical examination shows nearly always some compression of the liver cells at the periphery of the nodule, distinct evidence of an expansive growth.

But it is only in the more slowly growing forms that independent or expansive growth is at all marked. With a higher degree of malignancy the great mass of the tumour results from the invasion and destruction of the adjacent structures, indeed, we find the stroma in the central parts lagging behind the more active parenchyma, which, deprived of

the necessary nourishment, dies. It is to the central death of the cells, with the subsequent slow replacement by fibrous tissue, that the umbilication of superficial tumours, an important sign in the differential diagnosis between neoplasms and inflammatory formations such as gummata, is due.

Whatever its origin may be, whether intrinsic or extrinsic, we find the stroma varying considerably in character in different classes of tumours.

Its composition is always quite simple, consisting only of fibrous connective tissue and blood vessels, but the amount of formed fibrous tissue, the number and activity of the fibroblasts, and the richness of the vascular supply all differ within very wide limits.

As a rule, we find an abundance of stroma in the carcinomata derived from epithelium which normally possesses a rich connective tissue investment, and *vice versâ*. Thus, the breast is an organ containing a large quantity of connective tissue, and carcinomata of the breast have usually a plentiful well-formed stroma. Again, there is little supporting tissue in the normal liver, and primary liver-cell carcinomata have but a scanty stroma, but bile duct carcinomata are of a more scirrhous type, for the hepatic bile ducts are enclosed in a distinct fibrous tissue sheath The rule, however, is only of general application; many other factors, of which the most important is the rate of growth, combine to modify it Where growth is slow the stroma is dense and abundant; in the more rapidly progressing tumours the stroma becomes less and less marked, till in some cases the groups of cancer cells are supported by nothing stronger than delicate capillary blood vessels.

The activity of the fibroblasts is influenced very strongly by the tumour cells, and sometimes the stroma may be excessively cellular. Frequently also there are present numbers of adventitial cells; these are for the most part contained in the stroma, but they may penetrate into the parenchyma, insinuating themselves among the tumour cells. They are chiefly seen at the advancing margin of the growth, and are particularly evident on the deep surface of tumours derived from the surface epithelium.

This **cellular infiltration** consists almost entirely of lymphocytes and plasma cells, though a few eosinophil cells are sometimes to be seen, and an occasional mast cell.

It appears to be in the nature of a reaction to the growth, but it is by no means constant in its presence. The source of the cells is somewhat obscure, and it is still uncertain whether they are brought to

the tissue by the blood stream or by the lymphatics; there is at any rate no comparable change in the blood picture.

Should the tumour become ulcerated there is usually an active infiltration with polymorphonuclear leucocytes in the part, and this may be accompanied by so strong a reaction on the part of the stroma as to obscure almost completely the character of the growth.

Apart from ulceration, polymorphonuclear leucocytes occur but rarely in carcinomata.

Attention has already been drawn to the presence of occasional eosinophil cells in the zone of cellular infiltration. Although they are seldom a prominent feature, tumours are sometimes encountered where they are present in such enormous numbers as to dominate the histological picture (Fig. 52). This occurs chiefly in squamous carcinomata, though it occurs in several different varieties of this type of tumour, in carcinomata of the cervix uteri, the lip, the tongue, and the pharynx. It is doubtful what significance should be placed on this phenomenon, but it is certainly more than a purely local effect, for it is accompanied by a pronounced eosinophilia of the circulating blood which disappears should the tumour be extirpated.

The only other constituent of the stroma to be mentioned is the giant cell. This is of the "foreign body" type, and is seen almost exclusively in the more chronic squamous carcinomata. In these tumours giant cells may be present in considerable numbers in the neighbourhood of the larger masses of keratin, where they play the part of phagocytes or scavengers of the dead tissue.

Turning now to a detailed study of the various types of carcinoma, we find ourselves confronted with a great mass of tumours, derived from all the epithelial tissues of the body, and exhibiting correspondingly wide variations in gross and minute structure.

It is obviously necessary, therefore, to adopt some scheme of grouping in order to simplify our task; but this is not very easy to do.

There are, of course, three main sources of origin to any one of which a carcinoma may be traced: (*a*) the lining or glandular epithelia; (*b*) the cells of innocent epithelial tumours, adenomata, and papillomata; and (*c*) epithelial rests; and it might be possible to model a classification on these lines. There are, however, obvious difficulties in this course. It implies an ability to distinguish in every case the derivation of the cancer cell from its morphology, which we are far from possessing, it assumes that all tumours of any particular epithelium are similar in their structure, which is not true; and it depends upon theories which have not yet received universal acceptance.

FIG. 52 Microscopic section of a squamous-celled carcinoma of the pharynx, showing dense eosinophile-celled infiltration of the stroma. (1) Carcinoma cells ([illegible]), (2) eosinophile cells.

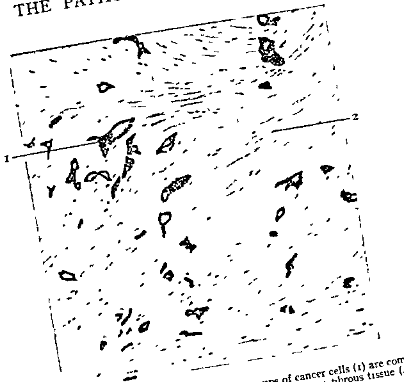

Fig 53 Scirrhous carcinoma of the breast The groups of cancer cells (1) are compressed and separated from one another by an abundance of dense fibrous tissue (2).
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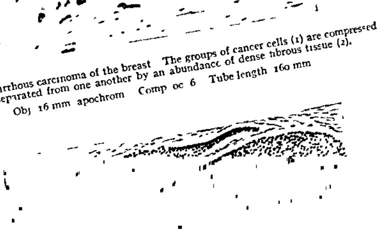

Fig 54 Microscopic section of an axillary lym Secondary to th the form of a medullary carcinoma which Fig 53 was drawn
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extent the amount of stroma which surrounds them, but a cancer growing in and infiltrating an already hard and mastitic breast may only be a scirrhous growth by the accident of the nature of the soil in which it is growing.

Again, mucous carcinomata do not always exhibit in every part a similar degree of mucoid degeneration, nor is the condition always present in tumours of any particular type of epithelium.

A. Carcinomata of Lining or Protective Epithelium

The tumours of this group arise from the skin, the mouth, the pharynx, the œsophagus, the lining of the pelvis of the kidney, the ureter, the bladder, the vagina, and cervix uteri. These are all situations invested by stratified or transitional epithelium, and the tumours are all classed together as squamous-celled carcinomata, though they exhibit marked differences according to whether they originate in a complicated structure like the epidermis, or in a simpler epithelium such as that lining the bladder

The histological features of a typical **squamous-celled carcinoma** of the skin are extremely characteristic. The tumour consists of broad branching columns or large solid masses of cells which include representatives of the various elements present in the parent epithelium. Thus, in the larger masses the peripheral cells are smaller than the central ones, they stain more deeply, and are joined together by a system of delicate protoplasmic bridges to which the name " prickle cell " is due. The central or older cells tend to exhibit degenerative changes similar to those seen in the normal epithelium. They become larger and clearer, and some of them are loaded with granules of eleidin. Finally, in the oldest cells of all, degeneration is complete, and the interior of the mass is occupied by keratinised or horny cells which form the " cell-nests," or " epithelial pearls " that are usually regarded as being the distinguishing mark of the squamous-celled carcinoma (Figs. 55 and 56).

These, then, are the diagnostic features of this variety of tumour: the presence of prickle cells, of cells containing eleidin granules, and of keratinisation. But it must be remembered that they are only pronounced in comparatively slow-growing tumours, with a greater rapidity of growth they may be modified very considerably.

In the first place, it is quite common to see a tumour which exhibits no granular cells at all, and although keratinisation is seldom absent altogether, it may be only rudimentary in the greater part of the growth. Again, the intercellular bridges may be absent or imperfectly

FIG 55 Squamous-celled carcinoma of the cheek (1) Stroma; (2) massive columns of epithelial cells showing (3) keratinisation and cell nest formation

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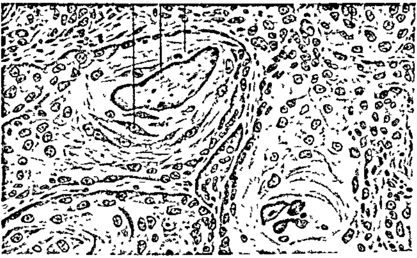

FIG. 56 Microscopic section of a squamous-celled carcinoma of the tongue (1) Prickle cells, (2) clear cells corresponding to stratum lucidum, (3) central masses of keratinised cells, (4) cells containing eleidin granules and representing cells of stratum granulosum.

Obj 8 mm apochrom Comp. oc 6 Tube length, 160 mm.

formed, so that true prickle cells are present in very small numbers Therefore, although from a general consideration of the shape, size, and arrangement of the cells we may have no doubt as to the real nature of a tumour, an absolute proof may be difficult to establish.

This is particularly so in the tumours of the œsophagus and pharynx. In the antrum of Highmore, also, there occurs a squamous carcinoma which may be extremely atypical.

Even in the more characteristic growths of the skin and the tongue we may meet with unusual appearances in association with a high degree of malignancy. The common rounded type of cell may be replaced by one in which the cytoplasm is drawn out and compressed into a spindle, and areas of the tumour may bear a striking resemblance to a spindle-celled sarcoma (Fig. 57) Or the cells may become

FIG 57 Microscopic section of squamous celled carcinoma of the pharynx, showing *spindle celled appearance of the epithelial cells In other parts of the section quite typical "cell nests" are formed*

Obj 16 mm apochrom. Comp oc 18 Tube length, 160 mm

polygonal in shape, and assume a trabecular arrangement ; this is seen in rapidly growing tumours infiltrating a tissue such as muscle (Fig. 58). Apart from these extreme deviations from the usual, it is not uncommon to find very marked differences in the size and shape of the cells Large multinucleated forms may be seen, and various kinds of cell inclusions are quite numerous

Besides the common squamous-celled carcinoma or "epithelioma," there is another interesting type of tumour derived from the skin. It is known in this country as the **rodent ulcer**, but on the Continent it is more often termed the **basal-celled carcinoma**, in the belief that it grows from the basal cells of the epidermis. This tumour is compara-

tively innocent, for although its growth is infiltrative, it scarcely ever forms metastases. It is composed of large solid masses of cells of an

FIG 58 Section of a squamous-celled carcinoma of the tongue invading muscle. (1) Columns of carcinoma cells growing in long trabeculæ among (2) striated muscle fibres.

FIG 59 Microscopic section of a rodent ulcer (1) Surface epithelium, (2) massive branching columns of epithelial cells
Obj 16 mm apochrom Comp oc 6 Tube length 160 mm

oval or even spindle shape, which are entirely devoid of prickles, and rarely become keratinised. It is also quite characteristic for the external layer of cells to be distinctly columnar *in shape* (Fig. 59).

There is considerable doubt as to the origin of these tumours. The generally accepted view is that they are derived from the hair follicles, but some authorities would trace them to the sweat or sebaceous glands, and it seems probable that they may arise from any of these sites or most commonly from epidermis itself.

While it is undoubtedly desirable to recognise the rodent ulcers as a distinct class of epidermal carcinomata, since they differ very plainly both histologically and clinically from the squamous-

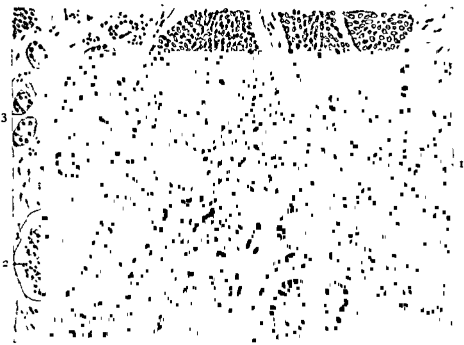

FIG. 60 Transitional celled carcinoma of the renal pelvis invading the kidney (1) Broad columns of malignant epithelial cells, (2) glomerulus, (3) renal tubules
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celled carcinomata, there seems to be a tendency to lay undue stress on this distinction. For tumours presenting very anomalous features are occasionally met with; in parts they show the typical histology of a rodent ulcer, but elsewhere they resemble very much more a squamous-celled carcinoma. If we regard the rodent ulcers as being derived from the basal layer of the epidermis, we cannot deny to their parent cells the potentialities of ordinary squamous epithelial cells, including the power of being able to give rise to a squamous-celled carcinoma; and if we refer their origin to the hair follicles, we are dealing with cells of but a slightly higher degree of differentiation.

With regard to the carcinomata of the simpler epithelial membranes

we find that they have a much less complicated structure. A carcinoma of the urinary bladder, for example, is composed of large islands of cells of the transitional or stratified type, but prickle cells are absent, and there is very rarely any distinct horny degeneration (Figs. 60 and 61).

The metaplastic potentialities of epithelial cells are very clearly revealed in the squamous-celled, or mixed squamous-celled and glandular carcinomata occurring in regions lined by columnar epithelium (Fig. 62). Such tumours are rare, but they have been found in several situations, notably in the gall-bladder and the uterus. Their

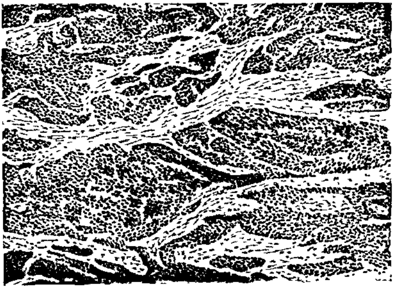


FIG. 61 Microscopic section of a transitional celled carcinoma of the urinary bladder Obj 16 mm apochrom Comp oc 4 Tube length, 160 mm

origin has been the subject of much debate, but it is now generally agreed that they are genuine instances of metaplasia, or alteration in type, of the columnar epithelial cells of the organ concerned. In these tumours the change is from columnar to squamous epithelium; the possibility of the reverse change taking place has not received universal acceptance. One occasionally has the opportunity of examining a squamous-celled carcinoma in which definite alveoli, lined by a single layer of cubical cells, are present. But there is always the possibility of the tumour being a primary glandular carcinoma—maybe, a sweat gland carcinoma—with secondary metaplasia to squamous epithelium.

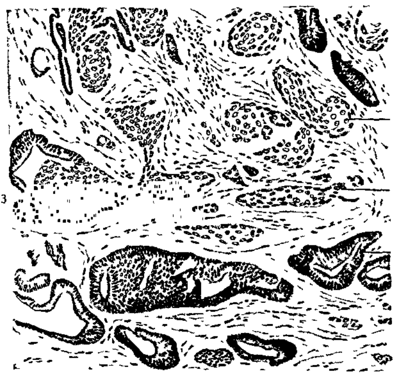
The question is probably impossible of solution by the study of the tumours as they appear in the human subject, but it has been worked out with great completeness in the case of the mouse (p. 48).

B. Carcinomata of Glandular Epithelium

This group may be subdivided into two according to the degree of differentiation of the tumour cells:

(*a*) Carcinoma simplex: composed of polygonal or spheroidal cells, destitute of any glandular arrangement.

(*b*) Glandular carcinomata: composed of columnar or cubical cells arranged in alveoli or tubules, or in such a manner as to recall the



FIG

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structure of the parent gland. They are known under a variety of names: adenocarcinoma, columnar-celled carcinoma, duct carcinoma, and malignant adenoma.

(*a*) **Carcinoma Simplex.** This tumour is seen to perfection in the mammary gland, but is by no means peculiar to this organ, for in many other situations carcinomata may grow whose cells show an equal lack of differentiation.

The cells of the growth are more or less spheroidal in shape, hence the name "spheroidal-celled carcinoma" by which they are often

known ; but they are very commonly distorted by mutual pressure into an irregular polygonal form. They have a fairly abundant granular cytoplasm, and a nucleus rich in chromatin. Inequalities in size and shape of both cells and nuclei are not uncommon, and cell inclusions may frequently be observed.

The cells are grouped together in solid alveoli or columns of varying width, and are supported by a connective tissue stroma which may be dense and abundant, or delicate and sparse (Fig 63). In some tumours the acini may be extremely large, and separated by only the scantiest connective tissue framework (Fig. 64) ; in others the stroma is increased

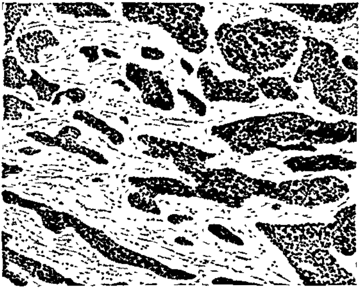

FIG 63 Microscopic section of a carcinoma simplex of the breast The tumour consists of undifferentiated epithelial cells arranged in alveoli or branching columns There is a moderate amount of fibrous stroma

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out of all proportion to the cancer cells, which are compressed into narrow strands. In the former class there is often evidence of great activity, karyokinetic figures may be numerous, while in the centre of the acini the nuclei are often fragmented and degenerated ; in the latter the cells have distinctly a more quiescent appearance.

Since these structural differences reflect with some accuracy the degree of malignancy of the tumours, there is justification for distinguishing the two types by the names "encephaloid" and "scirrhous." But it must be remembered that the proportion of connective tissue to epithelium is not always constant in the same growth ; an encephaloid tumour practically always remains cellular, but a scirrhous growth may at any time show a diminution in the

FIG 64 Section of a carcinoma simplex of the breast of the "encephaloid" type The cells are arranged in large acini, and there is only a scanty connective tissue stroma.

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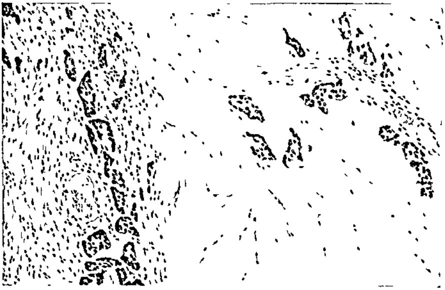

FIG 65 Microscopic section of a scirrhous carcinoma of the rectum The tumour cells show no differentiation, and the stroma is very abundant On the right hand side of the figure the fibrous tissue is extremely dense and acellular.

Obj 16 mm apochrom Comp oc 6 Tube length, 160 mm

amount of stroma, with increased activity of the epithelium. Further, it must be emphasised that a "scirrhous cancer" is not necessarily a carcinoma simplex; a superabundance of stroma may be seen also in the glandular and squamous-celled carcinomata (Fig. 65).

It is reasonable to assume in the life history of a tumour that its cells may alter from time to time in their character; at one period they may be "indifferent," at another they may attain to a higher degree of differentiation. At any rate, we may often notice a transition,

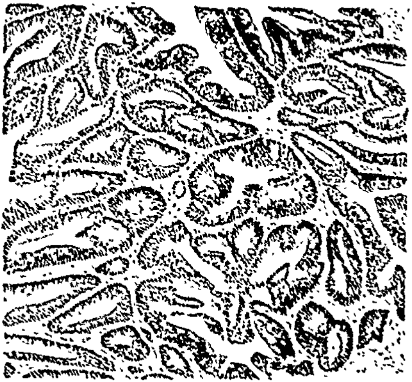

FIG. 66.—Microscopic section of a malignant adenoma of the rectum. The tumour cells possess a high degree of differentiation, and their form and arrangement indicate their glandular origin.

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gradual or abrupt, to an adenomatous structure in the carcinoma simplex, both in the primary growth and in the metastases.

(*b*) **Glandular Carcinoma.** This group has a wide distribution, and the individual members naturally have a varied structure.

The form and arrangement assumed by the cells is influenced to some extent by the characters of the parent epithelium, but even more by the degree of malignancy they possess. Generally speaking, the more malignant a tumour is, the more "indifferent" are its cells, though a slowly growing scirrhous carcinoma may show little evidence of a glandular origin.

Fig. 67. Section of an adenocarcinoma of the gall bladder. The tumour cells are very irregular in their form and arrangement. Obj. 16 mm apochrom. Comp. oc. 6. Tube length 160 mm.

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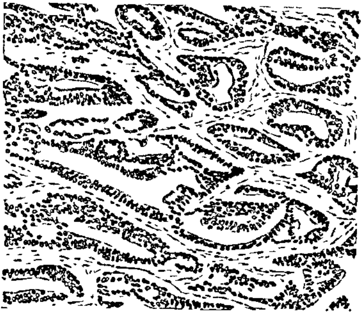

FIG 69 Section of a columnar celled adenocarcinoma of the breast
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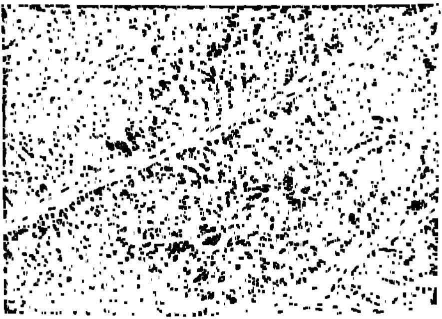

FIG 70 Section of an adenocarcinoma of the rectum The tumour is solid and the cells are not highly differentiated, but every now and then there is a suggestion of a tubular formation
Obj 8 mm apochrom Comp oc 6 Tube length, 160 mm

We can distinguish, therefore, all forms between the malignant adenoma in which the glandular structure of the parent epithelium is almost perfectly reproduced, and the more anaplastic adenocarcinoma which gradually passes into the carcinoma simplex (Figs. 66–70).

The cells may be columnar or cubical, and are commonly irregular both in shape and size. The nuclei are relatively large, but the cell bodies are smaller and denser than normal, especially in the columnar-celled forms

The acini or tubules are never quite regular, and often vary very much in size and outline. They may be lined by a single row of cells, or the cells may be heaped up into two or more layers. Occasionally the alveoli are dilated into microscopic cysts, and these may become filled by a papillary ingrowth of the lining cells, forming the **malignant papillary cystadenoma** (Fig 71).

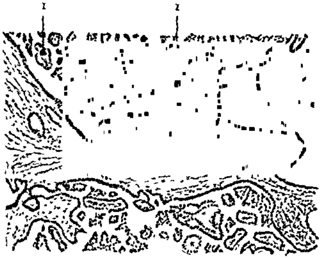

FIG 71 Microscopic section of a malignant papillary adenoma of the kidney. The section includes part of two large cysts which are loosely filled with papillary ingrowths of the lining cells. In places there is a slight deposition of calcium salts (1).

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Columnar-celled carcinomata often contain mucus-secreting goblet cells ; but this is not always so, and some intestinal carcinomata may be entirely devoid of such secretion. Similarly, carcinomata of the liver and the thyroid gland may or may not contain bile or colloid material respectively.

Variations in the amount and character of the stroma are seen in different examples of this class of carcinoma, as in the squamous-celled and simple types, in response to influences which have already been indicated

Retrograde changes are not uncommon in the carcinomata, and are sometimes of considerable importance. They have been discussed in a previous section (p. 15), and it is unnecessary to refer to this again.

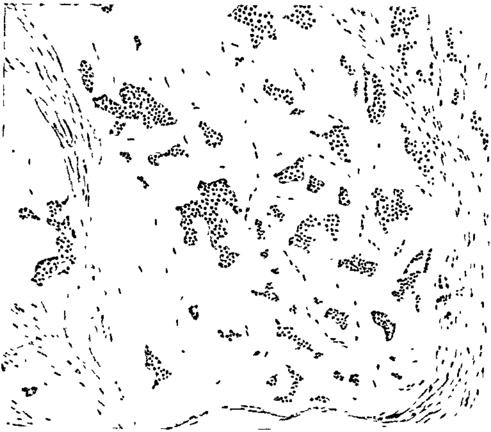

FIG 72 Section of a colloid carcinoma of the breast The tumour cells are grouped together in small alveoli which are surrounded by myxomatous tissue Broad bands of fibrous tissue traverse the growth at intervals

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FIG 73 Microscopic section of a colloid carcinoma of the cæcum (1) Normal mucous membrane; (2) muscularis mucosæ, (3) carcinoma acini surrounded by mucoid tissue.

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Polymorphism in Carcinomata

Although the majority of carcinomata are fairly characteristic in their structure, and can be recognised without much difficulty as epithelial blastomata, from time to time atypical forms are met with in which the tumour cells exhibit a varying degree of polymorphism which may be so extreme as to make the correct classification of the growth a matter of the greatest difficulty.

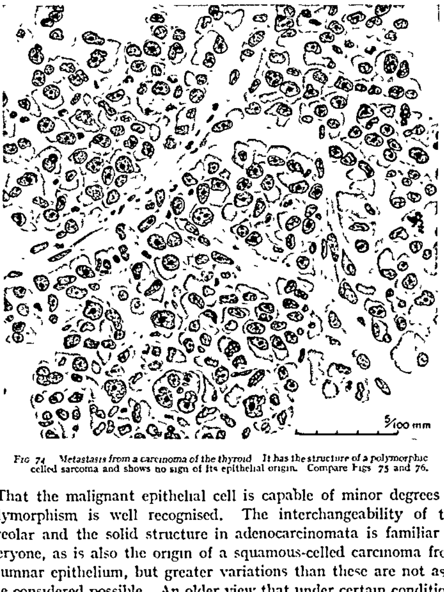

Fig 74 Metastasis from a carcinoma of the thyroid It has the structure of a polymorphic celled sarcoma and shows no sign of its epithelial origin. Compare Figs 75 and 76.

That the malignant epithelial cell is capable of minor degrees of polymorphism is well recognised. The interchangeability of the alveolar and the solid structure in adenocarcinomata is familiar to everyone, as is also the origin of a squamous-celled carcinoma from columnar epithelium, but greater variations than these are not as a rule considered possible. An older view that under certain conditions epithelial cells may actually be converted into connective tissue

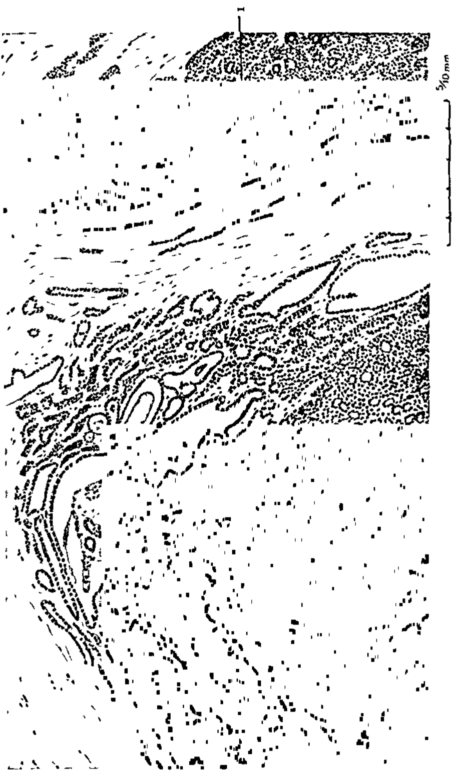

FIG. 75. Part of the primary carcinoma of the thyroid illustrated in Figs 74 and 76. The tumour cells form vesicles which contain colloid. At (1) the cells lose their differentiation and grow as solid trabeculæ.

elements has not found general acceptance, and the doctrine of the specific nature of cell growth is not seriously questioned. But even if such a degree of metaplasia is impossible, there can be no doubt that

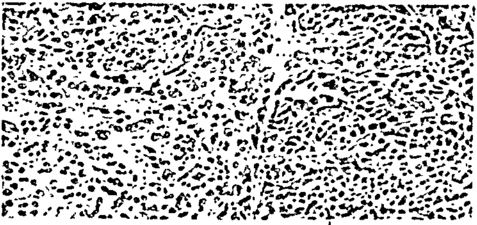

Fig. 27. A metastasis from the [illegible]

[illegible]

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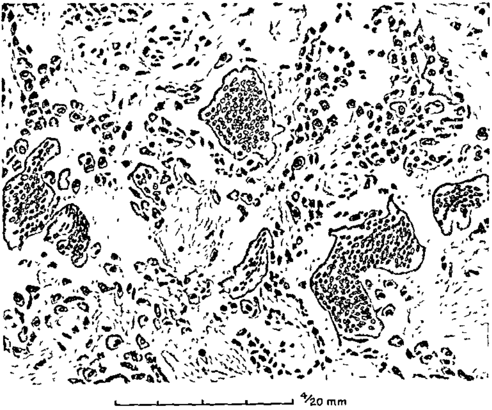


FIG. 78. High-power figure of the stroma of the carcinoma illustrated in Fig 77

FIG. 79. Showing the formation of the cellular "sarcomatous" *stroma of the* tumour (Fig 77) by the loosening and fraying out of the carcinoma cells.

of this power of polymorphic growth is particularly important in the study of the so-called carcino-sarcomata, or "mixed tumours," a few instances of which have been recorded. These tumours are essentially carcinomata in which the stroma has sarcomatous properties, and bear a close resemblance to the mixed tumours which develop in the course of propagation of carcinomata in mice (p. 48). But whereas it is possible by repeated transplantations to analyse the experimental

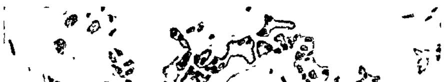


FIG 80 Showing the formation of the stroma giant cells of the tumour (Fig 77) from the carcinoma cells

tumours successfully, and to determine exactly what the anomalous histological structure represents, this line of investigation is impossible in human tumours In them the diagnosis rests entirely on the microscopic examination, and it becomes all the more necessary, therefore, to subject the histological findings to the most careful scrutiny.

Although it is probable that many of the carcino-sarcomata recorded are true mixed tumours, it is certain that some are examples of extreme polymorphism of carcinoma cells

The possibilities of which the malignant epithelial cell is capable in this direction are illustrated in Figs. 74 to 83.[1]

Figure 74, drawn from a section of a malignant growth of the

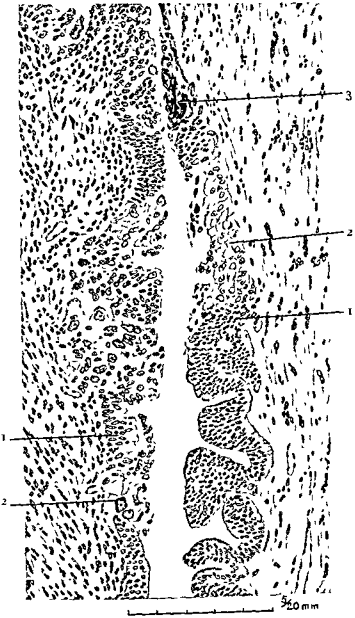


FIG. 81 Section of an adenocarcinoma of the uterus showing *the transformation* of the columnar cells (1) to squamous epithelium (2) which keratinises (3) There is a highly cellular spindle- and giant-celled stroma

thyroid, illustrates the structure of the greater part of the tumour which was originally diagnosed as a polymorphic-celled sarcoma.

[1] See also Kettle, "Polymorphism of the Malignant Epithelial Cell," *Proc Royal Soc Med.*, 1914, **12**, 1

A more extensive examination, however, revealed the true nature of the tumour. Fig. 75 shows the tumour cells differentiating and forming vesicles which contain "colloid," this structure being combined with a solid alveolar or trabecular type of growth. In Fig. 76, the transition from the solid trabecular to the loose "sarcomatous" type of growth is illustrated. This tumour, then, is not a carcino-sarcoma, but is a carcinoma of the thyroid exhibiting extreme polymorphism.

Fig. 77 illustrates an adenocarcinoma of the breast in which the stroma has the structure of a polymorphic or giant-celled sarcoma (Fig. 78). This stroma, however, really represents atypical growth

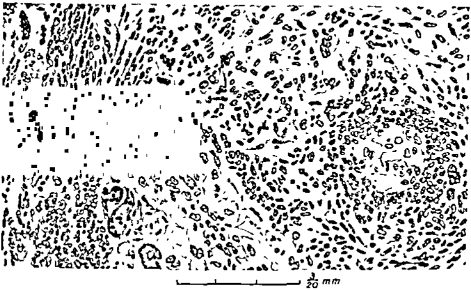


FIG. 82. Section of the tumour illustrated in Fig. 81 showing the squamous-celled type of growth and the formation of the cellular "sarcomatous" stroma by the fraying out of the carcinoma cells.

of the carcinoma cells. Fig. 79 shows the fraying out and loosening of the "stroma" cells from the periphery of carcinoma alveoli, and in Fig. 80 the giant cells are seen to be formed by the fusion of the carcinoma cells with proliferation of their nuclei.

Fig. 81, drawn from a malignant polyp of the uterus, shows the transition of columnar to squamous epithelium, and the cellular, "sarcomatous" stroma. This "stroma," again, really represents the polymorphic growth of the carcinoma cells (Fig. 82).

Fig. 83 is drawn from a carcinoma of the prostate which disseminated as a pure adenocarcinoma in the iliac glands, and as a mixed adeno-squamous carcinoma in the liver. The figure shows the transition of the adenocarcinoma into the squamous-celled carcinoma, and, in addition, the highly cellular "sarcomatous" stroma. This "stroma"

is actually formed by the loose, atypical growth of the squamous-celled elements of the carcinoma.

These tumours lend themselves fairly readily to histological analysis,

Fig ... There is direct transformation ... e stroma is cellular and "sarco ... cal, polymorphic growth of the

and their true nature can be determined with some degree of certainty. Other "mixed tumours," however, are much more difficult, and in them an absolute diagnosis may be impossible.

But, since the neoplastic epithelial cell can exhibit these remarkable powers of polymorphic growth, it is necessary to study any anomalous carcinoma with the greatest care before indulging in a diagnosis of "mixed tumour." Above all is it necessary to exercise restraint in drawing broad conclusions from the study of human material, for microscopy, our only available method of investigation, may mislead us.

TUMOURS OF NERVOUS TISSUE

It is necessary to recall the origin and development of the nervous system in order to follow a description and histological classification of its tumours.

The cells of the nervous system are derived from the medullary epithelium forming the medullary tube, which develops in the medullary plate: a strip of thickened ectoderm. With the exception of microglia and mesodermal cells which accompany the blood vessels, all the cells of the central nervous tissue develop from this epithelium. And all of them lose their epithelial characters except the cells which line the ventricles and canals or those which cover the choroid plexuses. The medullary epithelium is at first a single layer, but soon round germinal cells appear between the epithelial cells; these proliferate rapidly and collections of them become separated off to form neural crests. These are the precursors of the cranial and spinal ganglia and the peripheral nerves.

The columnar medullary epithelium lining the central canal is non-ciliated, but the cells which are differentiated to form ependyma develop cilia and blepharoplasts along their free border. But the cubical epithelium of the adult choroid plexus is free from cilia. The fixed ends of the ependymal cells may be prolonged into a neuro-fibrillary process The medullary epithelium differentiates to form medulloblasts, primitive spongioblasts and neuroblasts. Each of these is the forebear of other cells which in turn finally produce the numerous cells which make up the nervous system.

TUMOURS OF THE CENTRAL NERVOUS SYSTEM

As far as the brain is concerned the majority of tumours from this wide range of cells were until recently all grouped under the omnibus heading of glioma or glio-sarcoma. In 1926 Bailey and Cushing suggested a classification founded on a correlation of the type of cell found in the tumour with its counterpart in the brain or in a stage of its

development. This classification has proved serviceable in practice as it has been confirmed that the histological characters of a cerebral tumour give indications as to the prognosis and the best forms of treatment. The principles of the classification have been generally accepted and apart from slight modifications the classification is in general use.

The gliomata differ in the degree of their infiltration and destruction of the surrounding tissues, but this is not proportional to their cellular

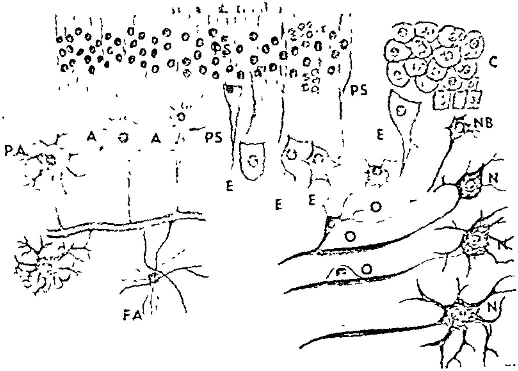


FIG. 84 Nerve cells.

A, Astroblast; P.A., Protoplasmic astrocyte; F.A., Fibrillary astrocyte; P.S., Primitive spongioblast; E, Ependyma; O, Oligodendroglia; N.B., Neuroblast; N, Neuron; C, Choroidal cells (Modified from Hortega.)

differentiation. The lethal effects of a tumour depend rather upon its position than its invasiveness, thus a well-differentiated circumscribed tumour may prove rapidly fatal because of its relation to vital centres or because in the adult the central nervous system is strictly confined by its bony walls and any increase in the intracranial pressure will result in compression of the brain. In a child the effects of increased intracranial pressure may be delayed by the stretching of the sutures and the growth of the bones of the skull.

A remarkable feature of the gliomata of the central nervous system

is that it is doubtful if metastases outside the system or its membranes ever occur. Tumours infiltrating the ventricular walls or the surface of the brain may spread throughout the leptomeninges but not beyond. Many of the tumours are extremely anaplastic and highly vascularised and on general principles might be expected to metastasise. To account for this failure to do so it has been pointed out that there are no true lymphatics in the central nervous system nor any connection with the lymphatic system so that no direct lymph node deposits can arise, and the veins of the central nervous system are structurally unfavourable for neoplastic invasion. It has also been suggested that

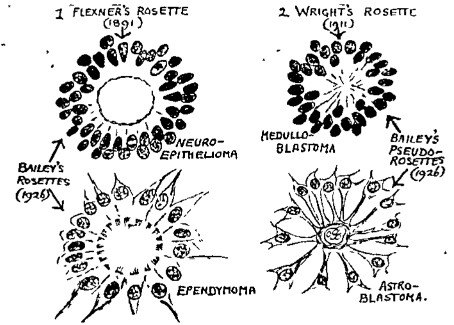


FIG. 85 Rosettes

neuroglial tissue is so specialised that it can only grow in a medium bathed in cerebro-spinal fluid; this hypothesis is unsatisfactory as tumours of sympathetic nervous tissue which are very similar to those of the central nervous system will grow and metastasise throughout the body.

The classification adopted here is largely that of Russell,[1] and is based upon the histological appearances of the majority of the cells forming the tumour.

It is probable that the tumours of the brain arise from neuroblasts, primitive spongioblasts, or medulloblasts, and not from fully differen-

[1] *Post Graduate Medical Journal*, 1939, 12, 150

tiated adult cells. The cells, having become tumorous, may continue to produce their like or may differentiate sufficiently to develop recognisable adult types of cell But it must be expected that in most brain tumours more than one type of cell will be found; the diagnosis is therefore based on the predominant cell type.

Neuroepithelioma. These tumours are rare in the central nervous system, but are not uncommon in the retina, where they have been

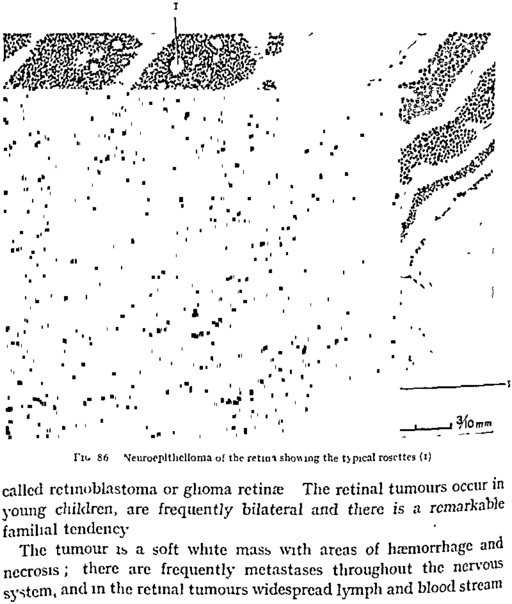


FIG. 86 Neuroepithelioma of the retina showing the typical rosettes (I)

called retinoblastoma or glioma retinæ The retinal tumours occur in young children, are frequently bilateral and there is a remarkable familial tendency

The tumour is a soft white mass with areas of hæmorrhage and necrosis; there are frequently metastases throughout the nervous system, and in the retinal tumours widespread lymph and blood stream deposits.

Microscopically they consist of sheets or bands of closely packed columnar cells with darkly staining nuclei; rosettes are often present; the cell margin of the lumen is free from cilia or blepharoplasts, but

is defined by a faint limiting membrane and there is a tendency to form blunt protoplasmic projections resembling the arrangements of the rods and cones of the normal retina. The rosettes consist of a central space around which cells are grouped, the cells are generally columnar with their nuclei near the base. No nerve fibres or neuroglia are present in the tumour.

Medulloblastoma is a tumour of which the histogenesis is much disputed although its features are well recognised. This neoplasm occurs most commonly in the first decade and appears to be confined to the cerebellum, where it forms a soft whitish tumour presenting in the midline and spreading into the roof of the fourth ventricle They frequently metastasise through the central nervous system either as a diffuse meningeal infiltrate or as isolated nodules on the spinal cord; they are moderately vascular and although invasive there is often a clear demarcation between the tumour and the cerebellum. They often induce internal hydrocephalus.

Microscopically they are very cellular consisting of small closely packed cells, containing relatively large round or oval nuclei having abundant dense chromatin and inconspicuous nucleoli. The cytoplasm is scanty and is sometimes drawn out on one side as an ill-defined tail They are sometimes grouped in spheres with the tails projecting inwards forming a pseudo-rosette. Usually many mitoses are seen and sometimes giant cells are present. Bailey and Cushing suggest that there is a differentiation to neuroblasts and spongioblasts, and that the tumour arises from medulloblasts which can differentiate in these directions.

Ependymoma is a tumour arising in the ventricular system and central canal of the spinal cord. The majority of these tumours are slow growing and of low grade malignancy but sometimes deposits are spread throughout the arachnoid. Macroscopically they vary from papillomatous growths of moderate size to massive tumours invading the adjacent brain substance.

Microscopically their characters have been carefully studied by Kernohan,[1] who has suggested that they should be subdivided into four types—choroidal papilloma, myxopapillary, epithelial and cellular ependymomata.

The **choroidal papilloma** simulates the normal choroid plexus closely; they are papillomata in which a core of vascular connective tissue is covered by cubical or columnar epithelium. The epithelium

[1] "Tumours of the Nervous System," *Assoc. for Research in Nervous and Mental Disease*, 1937, **16**, 182

is non-ciliated and there are no blepharoplasts, but the cytoplasm may be vacuolated; when present these vacuoles give the reactions for mucin. The connective tissue stroma serves to distinguish these

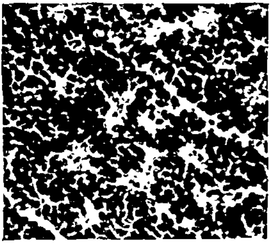


FIG. 87. Medulloblastoma cells grouped in rosettes of Wright

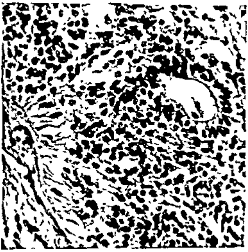


FIG. 88. Ependymoma: tube and cell processes inserted around a blood vessel.

FIG. 89. Ependymoma: rosette with fibrils in peripheral parts of cells.

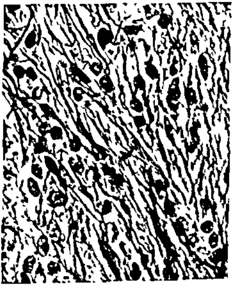


FIG. 90 Ependymoma: blepharoplasts indicated by arrows.

from papillary ependymomas in which the stroma always contains neuroglia.

The **myxopapillary ependymoma** has a superficial resemblance to the choroidal papilloma, but the tumour cells have all the characters of ependyma blepharoplasts (often centrally placed rather than at the free

edge) and the base of the cell is prolonged to form a heavy process attached to the vessels. The characteristic feature of this type is the myxomatous connective tissue stroma.

The **epithelial ependymoma** is a solid tumour in which the tumour cells may form tubes and are mostly arranged in groups with the processes of the cells inserted around the blood vessels. There is no mucoid degeneration or vacuole formation, but the cells may be ciliated and contain blepharoplasts.

The **cellular ependymoma** is similar to the epithelial variety save that there is no tubular formation, the perivascular pseudo-rosette is more marked and there may be eosinophil concretions. Some of the cellular ependymomata closely resemble oligodendrogliomata and Kernohan has suggested a close cytogenetic relationship between the two cell types.

FIG. 91 Choroidal papilloma.

There is little doubt that many of the brain tumours described as neuromedullo-epithelioma and neuroepithelioma are in reality well-differentiated ependymomata and that the confusion has arisen owing to a lack of appreciation of the characters of the ependymal cells.

Spongioblastoma multiforme (glioblastoma multiforme) is probably the commonest variety of glioma and following the appearance of clinical signs one of the most rapidly fatal.

Macroscopically the tumours are of considerable size and consist of an ill-defined soft whitish grey mass in which there are areas of old and recent hæmorrhage and necrosis ; there may be small cysts particularly in yellowish zones where hæmorrhage and necrosis has occurred. There may be considerable infiltration of the adjacent cerebral substance which is commonly œdematous. The liability to hæmorrhage within the tumour is a characteristic feature.

Microscopically the characteristic features are the great cellular variation and the vascular proliferation. The tumour shows no definite pattern, but consists of a complex of uni- and bi-polar spongioblasts often orientated around vessels to form pseudo-rosettes or in palisade formation and scattered amongst these are multinucleate giant cells ;

there may be areas of astrocytic proliferation, and in certain zones the astrocytic differentiation is such as to suggest to some histologists that these tumours are examples of anaplasia occurring in astrocytomata, rather than a poorly differentiated tumour with areas of mature cell types. Mitosis is frequently found in the giant cells and spongioblasts and there are large zones of necrosis and hæmorrhage with secondary proliferation of microglia.

The vascular changes, although sometimes seen to a minor degree in other gliomata, are a striking feature of the spongioblastomá multiforme. The tumour is richly supplied with vessels, and these show a considerable endothelial proliferation and hyperplasia with the production of angeiomatoid areas. In the arterioles the intima shows a similar proliferation and thromboses with recanalisation by atypical endothelial cells. The significance of this vascular change is not known, it might be neoplastic or more likely a reactive hyperplasia resembling that sometimes found in granulomata. Apart from diffuse infiltration it is sometimes possible to demonstrate an infiltration along axons or blood vessels, but meningeal spread is seldom observed.

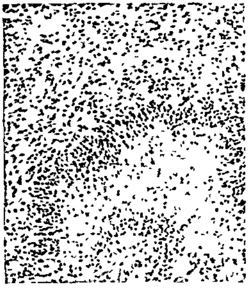


FIG. 92. Spongioblastoma (glioblastoma) multiforme

In some cases the tumours appear to be multicentric.

Spongioblastoma polare is an uncommon tumour which grows slowly to form a firm white sharply demarcated mass in which cysts may be present

Microscopically it is formed of an interlacing network; uni- and bipolar spongioblasts arranged in parallel bundles; a characteristic feature is the absence of neuroglial fibres and the lack of relationship between the tumour cells and the blood vessels. These tumours sometimes resemble the acoustic nerve tumours (v.p. 177) and may be found in cases of Von Recklinghausen's disease.

The existence of the polar spongioblastoma has been questioned by Russell as the result of tissue culture and she suggests that they may in reality all be astrocytomata.

Astroblastoma is an uncommon variety of glioma which forms an

ill-defined greyish-white tumour with areas of necrosis and cyst formation.

Microscopically it consists of a regular arrangement of astroblasts arranged in dense rows along the blood vessels and connective tissue stroma. The astroblast is a pyramidal cell with abundant protoplasm and one or two nuclei. From one pole of the cell a thick process extends to a blood vessel; a few fine processes arising from the other portions of the cell body extend in various directions. In a typical tumour there are no glial fibres other than those of mature astrocytes and mitotic figures are rare

Fig 93. Astroblastoma.

Astrocytoma is one of the commonest forms of brain tumour and probably the most benign. It is a smooth white tumour commonly ill-defined in adults, but often well-defined in children and varying from a rubbery hard to a gelatinous

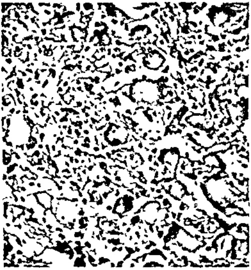


Fig. 94 Astrocytoma gemistocytic.

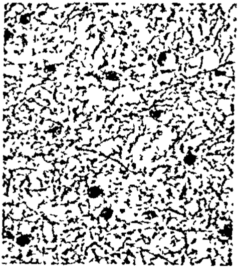


Fig. 95. Astrocytoma, diffuse type.

consistency. Cyst formation may be present and there is often a nodule of neoplastic tissue projecting into the cyst cavity, areas of calcification are sometimes found in the tumours.

Microscopically three main histological types can be recognised. In the pilocytic astrocytoma the tumour is made up of bundles of astrocytes with small nuclei and long slender neuroglial fibres often running in parallel sheaves through a fine interlacing network; cystic degeneration is most frequent in this form. The type cell of the gemistocytic astrocytoma resembles the "gemästete Zell" of Nissl which is normally found in chronic inflammatory cerebral lesions. The tumour consists of loosely arranged cells of this type with a rounded swollen cytoplasm and an eccentrically placed nucleus; there are short thick neuroglial processes projecting from the cell body to form a loose tangled network.

The third type is the astrocytoma diffusum in which the tumour infiltrates and causes great induration of large areas of the cerebral hemispheres and may be bilateral. They are formed of rather small cells which form an abundant network of intercellular fibrils. A characteristic feature of this type is that there is comparatively little destruction of neurones which are surrounded and displaced by the tumour cells. There is no clear demarcation between tumour tissue and normal brain substance, no degenerative changes, and it is only possible to determine the full extent of the tumour if whole slices of brain are examined with the aid of myelin stains.[1]

Oligodendroglioma is an uncommon tumour which grows slowly and is comparatively benign. It is clearly demarcated, firm, of greyish-red colour and frequently shows areas of calcification and cyst formation.

Microscopically it is formed of closely packed round or polygonal cells with little interstitial stroma. The nuclei are round, contain a dense chromatin net and are set centrally in a pale vacuolated cytoplasm. Mitotic division is not commonly seen, but silver impregnations reveal short cytoplasmic processes. The tumours are relatively avascular and degenerative changes are frequent, but in some forms there is a well-marked astrocytic and connective tissue stroma dividing the tumour cells into solid acini.

Gangliogliomata have only recently been recognised chiefly as a result of Globus' investigations.[2] These tumours are ill-defined, somewhat firm and granular and may show cystic changes; often they extend widely throughout the white matter and may spread along the main fibre tracts

Microscopically they are formed of a matrix of spongioblasts,

[1] See Waggoner and Lowenberg "Tumours of the Nervous System," *Proc Nerv Ment. Dis*, 1937, **16**, 371

[2] Globus, *Am J Cancer*, 1938, **33**, 163

astroblasts and astrocytes in which are lying atypical ganglion cells which are often multinucleate. They are not highly vascularised and degenerative changes may occur.

TUMOURS OF THE SYMPATHETIC SYSTEM

The tissue of the sympathetic system is derived from those portions of the primitive neuroectoderm which are separated off to form the neural crests; the neuroblasts spread along the anterior spinal roots to form the various plexuses and the suprarenal medulla. The neuroblasts differentiate to form sympathogonia, small darkly staining cells resembling lymphocytes which are commonly arranged in clusters and pseudo-rosettes. Further differentiation takes place with the formation of sympathoblasts—larger than the sympathogonia with a vesicular nucleus and a cytoplasm prolonged to form nerve fibrils—and ganglion cells In the medulla of the adrenal they form the chromaffin cells or phæchromocytes. Corresponding to these developmental stages sympathicoblastomata (neuroblastomata), ganglioneuromata and phæchromacytomata or chromaffin tumours have been described. The tumours of the sympathetic tissue may be found in the cervical, thoracic or abdominal region in relation to the ganglions or in the adrenals. The tumours are white, sometimes with areas of hæmorrhage and necrosis, and vary in consistency from the soft somewhat diffluent masses of the sympathicoblastomata to the firm fibrotic ganglioneuromata; when malignant they show a marked tendency to local infiltration and may form tumours of considerable size. The poorly differentiated growths metastasise widely to lymph nodes, liver and bones, but the ganglioneuromata seldom spread from the primary site.

Microscopically the **undifferentiated sympathicoblastoma** (neuroblastoma) is formed of masses of round cells closely resembling small lymphocytes with little arrangement save that in places they form spherical clusters; no neurofibrils can be demonstrated and the cytoplasm of the cells shows no projections; mitoses are frequent; the stroma is formed of thin-walled capillaries and there are collagen and reticulin septa radiating from the large vessels to form lobules, but there is no reticulin network between the masses of sympathogonia.

The **differentiated sympathicoblastomata** (neurocytoma) are formed of masses of sympathogonia and sympathoblasts which are larger cells with cytoplasmic projections which form fibrils which do not stain readily by the ordinary methods for axons. The sympathoblasts are often arranged to form rosettes and in some places poorly formed

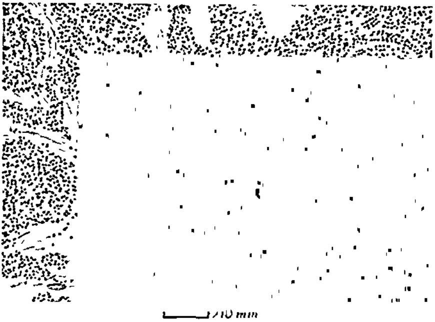


FIG. 96 Section of an undifferentiated sympathicoblastoma of the suprarenal showing the formation of fibrils

FIG 97. Ganglioneuroma of the suprarenal, showing nerve fibres and ganglion cells.

ganglion cells may be formed. The lobules of tumours cell may be separated by bundles of fibrils, but there is little reticulin stroma and a considerable liability to undergo necrosis or calcification.

The **ganglioneuromata** are made of mature type ganglion cells from which neurofibrils project into a stroma formed of neurofibrils, collagen and reticulin arranged in bundles; these tumours are relatively avascular and calcification is common, but necrosis is seldom seen; at the periphery of the tumours there is an increased density of the collagen stroma, but there is no true capsule formation.

The phæchromocytoma will be described with the tumours of the suprarenal gland (p. 301).

Tumours of sympathetic nerve fibres (neuromata) have been described in cases of appendicular fibrosis with obliteration of the lumen and more rarely in association with chronic gastric ulcers, but there is considerable difficulty in demonstrating actual nerve fibrils in these tumours and they probably represent hyperplastic processes rather than neoplasms.

TUMOURS OF THE NERVOUS SHEATHS AND PERIPHERAL NERVES

The brain and spinal cord are covered by the arachnoid and dura mater and the cranial and spinal nerves are covered by sheath of Schwann and perineureum both in their intra- and extra-thecal course, and neoplasms of varying character may develop in connection with all these membranes.

Meningeiomata

These tumours, which form firm circumscribed masses on the inner surface of the dura mater, have had many names indicating the varying views as to their histogenesis or cytology *Originally* described as meningeal cancers by Cruveilhier, Virchow called them psammomata (owing to the concretions which they frequently contain) and Golgi introduced the term endothelioma for them. More recently they have been called arachnoid or dural fibroblastoma or exothelioma, but there is little doubt that Cushing's non-commital yet descriptive meningeioma is the best name for them.

Meningeiomata are usually adherent to the dura mater from which they derive their abundant blood supply and may occur anywhere in the dural distribution, but are most frequently found in the cranium and at those points where arachoidal granulations are most marked. All grades can be found between arachnoid villi, clusters of arachnoid

villi and meningeiomata. They may cause considerable compression of the underlying brain substance and very rarely they penetrate the dura mater to infiltrate the adjacent bone. The bone over them is often thickened though seldom infiltrated. They grow slowly and do not metastasise, but unless removal has been complete usually recur locally.

Macroscopically they form rounded circumscribed tumours of varying size ; in consistency they are commonly firm, but may be extremely hard with calcareous particles or actual bone formation. The softer

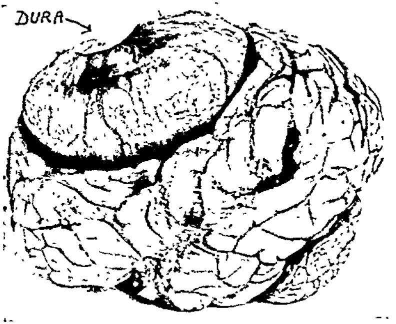


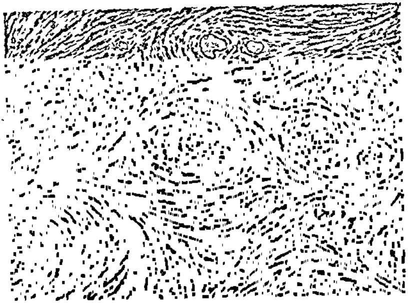
FIG. 98. Meningeioma of dura compressing brain.

forms may show areas of necrosis or hæmorrhage or yellowish areas indicating the presence of xanthomatous material.

Microscopically their structure is varied and they have been subdivided into numerous types, but the simple classification of Russell and Bland [1] is adequate. These workers recognise five forms—the "endotheliomatous," fibroblastic, angeioblastic, xanthomatous and myxomatous, but the vast majority fall into the first two categories.

The endotheliomatous form consists of large polygonal cells having boundaries which may be poorly defined or distinct and are grouped into lobules separated by thick irregular trabeculæ containing blood vessels. The nuclei are relatively large, have a delicate chromatin net and may have two or three nucleoli. The cells may appear in sheets,

[1] *J. Path. and Bact.*, 1938, **47**, 291.



FIG

Obj 8 mm, apochrom Comp. oc. 4 Tube length, 160 mm

FIG. 100. Microscopic section of an endotheliomatous meningeioma with formation of psammoma bodies lying in a loose connective stroma in which occurs groups of proliferated meningeal cells.
Obj 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

but in all of them there is a tendency to form whorls and in most the whorled pattern predominates. The trabeculæ may contain reticulin, elastic or collagen fibres. The central part of the whorls may degenerate, being converted into collagenous tissue which later may become calcified and form a psammoma body

There is no sharp distinction between the endotheliomatous and the **fibroblastic** forms. The characteristic examples are composed of interlacing bundles of long narrow spindle cells containing conspicuous fibroglial fibrils. The nuclei are elongated and rod-shaped and the whorled arrangement of the cells is less conspicuous and of a looser structure than in the endotheliomatous variety.

FIG 101. Meningeioma infiltrating skull

The **angeioblastic tumours** are densely cellular with numerous spaces lined by vascular endothelium of a hypertrophic type. Between the capillary blood spaces are cells similar to those in the first two varieties, but there is always a very rich interlacing network of reticulin fibrils throughout the tumour.

The **xanthomatous variety** resembles the "endotheliomatous" meningeioma save that many of the cells are "foam cells" containing much anisotropic lipoid.

In the **myxomatous form,** spindle or stellate cells lie in a loose myxomatous stroma poor in reticulin and collagen.

In many of the meningeiomata the tumour cells frequently show acidophil intranuclear inclusion bodies ; this was at one time thought to be similar to the inclusion bodies found in certain virus infections, but similar bodies have been found in normal adult and fœtal meninges.

Meningeal sarcoma has been described : it is certainly a rare tumour and in the majority of cases which have been examined critically it has been shown to be an extension from a cerebellar medulloblastoma.

TUMOURS OF THE PERIPHERAL NERVES

It is convenient to consider both the cranial and spinal nerves together for their histological character and tumours are *essentially* similar In the nerves a distinction between blastomatoid conditions

and true blastomata is almost as difficult as it is in the lymphoid organs. A nerve is made up of a large number of axons or neurites, each continuous from the ganglion cell to the end organ; there may or may not be a layer of myelin covering neurite, but surrounding the myelin sheath, if present, or the axon itself, is a syncytium of cells of Schwann, which it has been shown are the homologues of the oligodendroglia and are of neuroectodermal origin; outside the Schwannian syncytium is a thin layer of reticulin—the Plenk-Laidlaw sheath. Between the individual nerve fibres is an interstitial tissue—the endoneurium formed of interlacing cells with collagen and reticulin fibres running parallel to the nerves; surrounding the bundles of nerve fibres is a dense connective tissue sheath—the perineurium. The histogenesis of the *endoneurium* and perineurium is in doubt as is also the part which these fibres play in tumour formation.

After section of a nerve hyperplastic conditions arise which may simulate a neoplasm and a brief account of the changes that occur will be given as *it* has a direct bearing on the formation of certain nerve sheath tumours. **Traumatic Neuroma.** Section of a medullated nerve is followed immediately by Wallerian degeneration of its fibres. In the proximal stump the degeneration is limited to the tip, but it extends throughout the length of the distal portion and there is complete disappearance of the axons. About four days after section there is a considerable proliferation of the sheath of Schwann in both the proximal and distal portions. In the proximal portion this is accompanied by a regeneration of the myelin sheath and axons and there is an associated increase of connective tissue elements. In amputated limbs or injuries in which there has been a considerable break of continuity between the two ends this proximal proliferation becomes very marked and nodules of considerable size are formed. This is the true neuroma of Virchow. The distal portion of a divided nerve also shows a proliferation limited to cells of Schwann and forms a false neuroma or peripheral glioma which Masson[1] has shown is strictly comparable to the spontaneous nerve sheath tumour. When the neurites from the proximal end penetrate the distal portion, the proliferation of Schwann cells ceases and a myelin sheath develops, but there is considerable delay before the end organs are reformed and function restored.

Schwannoma (Neurilemoma; neurinoma; perineural fibroblastoma; peripheral glioma). This tumour, with its bewildering variety of names, may arise in connection with the cranial or spinal nerves and affects

[1] *Am. Jour. of Pathology*, 1932, 8, 364.

not only the larger nerves, but also the smaller branches, and it is probably most frequently found as a peripheral manifestation (subcutaneous tissue, palate, stomach, etc.). The tumours are commonly solitary, encapsulated and are seldom of any considerable size; where they are arising in connection with a sizeable nerve this will be found to be running at the side of the tumour, but in those arising in the subcutaneous tissue the naked eye relationship to a nerve cannot usually be made out. They grow slowly, are not painful unless by pressure, but may cause ulceration of the overlying tissues and, in the case of the intrathecal tumours, symptoms arise from damage to the adjacent structures.

Macroscopically the Schwannomata have a well-defined capsule; they are firm and their cut surface is smooth, greyish-white and semi-translucent. Cystic changes are frequent and this may vary from a few small areas to a cystic tumour in which the capsule alone is formed of Schwannian elements. Hæmorrhagic areas are sometimes found and yellowish areas of lipoid in intracranial tumours.

Microscopically the appearances are highly characteristic. The tumour is composed of a tissue varying in density by reason of an irregular degenerative process and the dense and less dense areas have been described as types A and B respectively.

The dense (type A) tissue is formed of a closely set network of reticulin fibrils with a tendency to a parallel arrangement, and lying on this are bundles of anastomosing spindle-shaped cells with a rod-shaped nucleus; between the individual cells and between the bundles is a varying amount of collagen; the spindle cells are arranged parallel one with another and a characteristic feature is that in certain zones the nuclei also lie in parallel bands producing a palisade effect. Sometimes the palisaded bundles may resemble a tactile corpuscle, but more commonly the gross arrangement is serpentine. The type B tissue has the same cellular components as the type A, but there is an extreme degree of interstitial œdema and microcystic change with a wide separation and disorientation of the cells and fibres. The resulting appearance of a Schwannoma is that of serpentine zones of parallel bundles of cells in palisade lying in an œdematous matrix The tumours are poorly vascularised and sometimes the collagenous change is great Nerve fibres are not found in the tumours, but may occur at the edge or in the capsule Malignant changes in a true Schwannoma is rare, and after complete surgical removal they seldom if ever recur.

There has been considerable controversy as to the actual nature of

the tissue elements involved in these tumours; one school, led by Penfield[1] believes that owing to the large amount of collagen present they must be derived from the mesodermic elements of the nerve sheath, the other school agrees with Masson that they are Schwannian in origin and that these cells have the ability to form collagen and reticulin. Recent critical histological analysis and tissue culture studies[2] have done much to support Masson's views.

Neurofibroma. In contrast to the Schwannoma, neurofibromata are

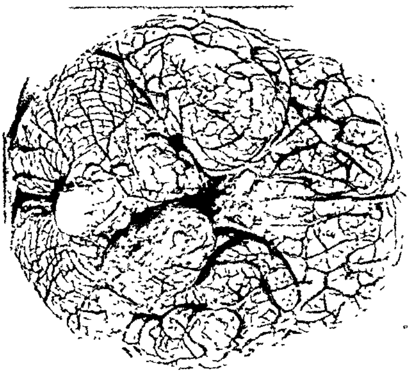


FIG 102 Acoustic Neurofibroma.

almost invariably multiple and are usually found in a complex systematised disease which may be familial and is associated with the name of von Recklinghausen. Neurofibromata are more akin to hyperplastic processes than true neoplasms and are variable in their form, though their relationship to a nerve can usually be made out. Commonly they form pinkish-grey circumscribed tumours in the course of a nerve which can be seen to enter and leave the tumour; in some cases the nerve appears normal in thickness immediately after its

[1] "Tumours of the Sheaths of the Nervous System" in *Cytology and Cellular Pathology of the Nervous System*, Sect XIX, vol 3, p. 958, New York, 1932.
[2] Murray and Stout, *Am J. Path.*, 1940, 16, 41.

emergence, but usually there is a diffuse thickening and tortuosity of the nerve gradually dwindling to a normal thickness. In the plexiform neuroma (cirsoid neuroma) a number of nerves become thickened, tortuous and elongated and form visible tumours, which on palpation give the impression of a collection of soft nodular anastomosing cords.

The neurofibromata are not adherent to surrounding tissues, but it is necessary to remove at least a portion of the affected nerve with the tumour ; they are not very vascular and on cross-section the tissue is firm with a granular surface ; gelatinous changes may occur, but cystic degeneration is unusual.

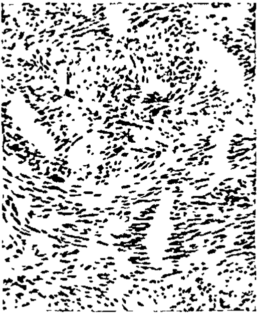


FIG 103 Schwannoma in von Recklinghausen's disease

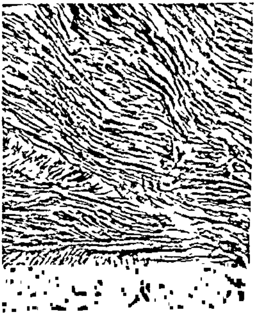


FIG 104 Schwannoma ; same as Fig 103 stained by *Laidlow's method*

Microscopically they show little definite pattern, but consist of a loosely woven tissue in which long spindle-shaped cells run in an irregular interlacing fashion and lie in a loose non-mucinous interstitial fluid. The cells are commonly of great length with a wavy outline and a clearly defined cytoplasmic edge. The nucleus is narrow and is invariably slightly curved in outline There is no tendency to anastomosis between the cells as is found in the Schwannoma nor is there any palisading serpentine bundle formation or microcystic degeneration Neurites with or without myelin sheath run through the tumour and the spindle cells are often orientated in relation to the axon The amount of collagen and reticulin formation is variable, but the reticulin never shows the definite pattern found in the Schwannoma.

In a nerve adjacent to a neurofibroma the main structures are maintained, but there is increased separation of the individual nerve bundles and fibres as the result of the cellular proliferation.

There is as much conflict of opinion as to the histogenesis of the neurofibroma as of the Schwannoma, in fact, the confusion is greater as many investigators have failed to distinguish between the two tumours. It is probable that the main if not the whole proliferation is Schwannian in origin, but the cells are of a more adult type, though showing less organoid arrangement; however, it would seem that mesodermic elements do play some part in the tumour formation.

Multiple neurofibromatosis or von Recklinghausen's disease is characterised by the presence of neurofibromata on a number of nerves and occasionally solitary Schwannomata, melanomata and pigmented patches on the skin; soft pedunculated skin tumours (molluscum fibrosum) which in some cases are peripheral neurofibromata, but in others appear to be pure fibromata, and these may sometimes form areas of diffuse skin thickening—elephantiasis neuromatosa, in which both neurofibromatosis and proliferation of sensory endorgans can be found. There may also be bony deformities with scoliosis and hypertrophy of the limbs and even hypertrophy of a portion of intestinal tract secondary to a regional neurofibromatosis.[1]

In its most complex form neurofibromatosis may be associated with meningeiomata, bilateral acoustic nerve tumours and gliomata,[2] and this association of neuro-ectodermic and mesodermic hyperplastic processes has lent support both to the school that would regard the meningeiomata as of neuroectodermal origin and that which believes that all nerve sheath tumours are of mesodermic nature. On the other hand a study of determinative embryology reveals the close interrelationship of proliferation of the various germ layers and there are numerous other examples of complex systematised dysplasia in which this occurs.

In a certain proportion of cases of neurofibromatosis the tumours undergo mailgnant change developing characters closely resembling fibrosarcomata, and the possible distinction between neurogenic sarcoma and the ordinary fibrosarcoma has already been discussed (v. p. 104)

[1] Th[illegible] ofibromatosis is well described by Carriere [illegible] Recklinghausen, G. Doin et cie, Paris, 1938, [illegible] i, p 1326, Arnold & Co, London, 1940.

[illegible] Worster-Drought, Carnegie Dickson and [illegible] Bailey and Hermann, *Am J Path*, 1938, [illegible] *J. Canc*, 1938, 32, 339

M 2

There are a very few instances of malignant tumours arising in peripheral nerves having the characters of a neuro-epithelioma (v. p. 162), which can only be explained on the basis of embryonic rests of the neural crest or the persistence of undifferentiated neuro-ectodermic cells in peripheral nerves.

THE MELANOMATA

The melanomata differ from all other tumours in that their cells contain a variable amount of an iron-free pigment called melanin. Most of them grow from two situations, the skin and the choroid coat of the eye, but they may be found in many other parts of the body such as the membranes of the brain, or the lower part of the rectum. *They are of great interest, not only from the diversity of their histo-*logical structure, but also from the point of view of their exact nature and origin.

This is linked with the origin and nature of the pigment bearing cells. In normal skin melanin pigment is found in the basal cells of the epidermis and sometimes in spindle cells resembling histiocytes in the dermis. Bloch in studying pigmentation of the skin found that if fresh tissue is placed in a buffered solution of " dopa " (dioxyphenylalanin) after a time certain cells in the basal layers of the epidermis will contain melanin. These cells were called melanoblasts because they could form melanin. The cells found in the dermis could not form melanin, but were carriers of preformed melanin ; they were called melanophores The epithelial cells (melanoblasts) were believed to be the essential cells ; the connective tissue cells, melanophores, were thought to be phagocytes which took up melanin preformed by the epithelial cells. This simple statement has been complicated by Masson's suggestion that the melanoblasts are not epithelial but neurogenic in origin. It is possible that both views are correct , there may well be epithelial cells and nervous cells in the skin and elsewhere which can produce melanin and melanomata

The cutaneous melanomata have been more extensively studied than the other forms, and illustrate very well the points at issue. The simplest example of a melanoma, the pigmented mole, is one of the commonest abnormalities of the skin. It is a congenital formation, and occurs as a small warty tumour of a brown or blackish colour ; some forms have a constricted base amounting almost to a stalk, but as a rule they are only slightly raised above the surface, and they may be quite flat *Microscopically*, the tumour has a very definite structure,

consisting of small groups of rounded, pigmented cells lying in a fairly dense fibrous tissue stroma; sometimes the cells may be seen to be congregated in the perivascular lymphatic spaces. The covering epithelium may show a papillomatous overgrowth, but it is more usually somewhat thinned and the papillary processes are often increased in size. Groups of the specific cells may come into very intimate contact with the columns of epithelial cells (Fig. 105). The amount of pigment is by no means constant; the majority of the cells may be loaded with golden brown granules, or only a few cells here and there may contain them.

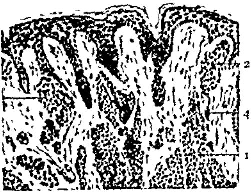


Fig. 105. Microscopic section of a pigmented mole. The tumour consists of groups of spheroidal

Obj. 8 mm apochrom. Comp. oc. 4. Tube length, 160 mm.

Whatever may be the origin of the melanoblast, it is quite certain that from them are derived those highly malignant tumours known as melanotic sarcomata, nævocarcinomata or melanocarcinomata.

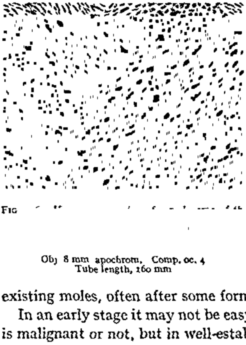


Fig.

Obj. 8 mm apochrom. Comp. oc. 4. Tube length, 160 mm

For no apparent reason, or perhaps as the result of some chronic irritation, a pigmented mole may assume an active growth, projecting above the surface of the skin, and frequently becoming ulcerated. With the increased rapidity of growth the histological appearances are markedly changed; the tumours become much more cellular, and the cells themselves present evidence of a heightened activity.

Sometimes these tumours may develop apart from preexisting moles, often after some form of trauma.

In an early stage it may not be easy to determine whether the growth is malignant or not, but in well-established cases the diagnosis is quite

clear. It may still be difficult, however, to decide as to the nature of the tumour, for two distinct histological types exist. In the one the structure, apart from the presence of melanin, is that of a spindle-celled sarcoma (Fig. 106); in the other the cells are polygonal or spheroidal in shape and have a solid acinar arrangement of a carcinoma (Fig. 107). Sometimes, even, a definitely adenomatous or acinous formation obtains (Fig. 108).

So marked are the histological differences that some authorities recognise two separate forms of pigmented neoplasms, the melanotic sarcoma and the melano- or nævo-carcinoma; the former arising from

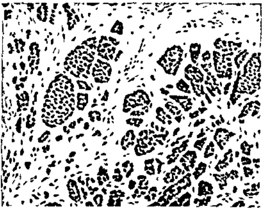


FIG. [illegible]

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Tube length, 160 mm

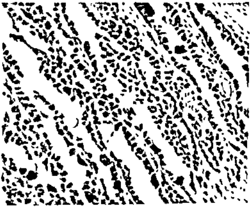

FIG. [illegible] of pigment.

Obj 8 mm. apochrom Comp oc 4.
Tube length, 160 mm

connective-tissue melanophores, and the latter from the rete Malpighii of the epidermis or melanoblasts

The differences are, however, more apparent than real; tumours frequently exhibit all stages between the two types, and there seems no doubt that all melanomata are forms of one and the same class of new growths. Further, the acceptance of Masson's views makes it readily understandable that the character of the tumour may vary from a fibrillary Schwannoma-like growth to one in which the cells more closely resemble the nævus cell.

Both types may be met with in the skin, but the melanomata of the eye are nearly always composed of spindle-shaped cells.

A prominent feature in the melanomata is the rapidity with which they disseminate, and the number and size of the metastases A trivial, almost unnoticed, primary tumour may give rise to innumerable

secondary growths affecting practically all the organs of the body. Dissemination by way of the lymphatic channels frequently takes place, especially in the cutaneous tumours; and the liver is particularly prone to be the seat of metastases, though these may be slow in declaring their presence. It is common to find melanin containing cells in the arachnoid over the medulla and occasionally the whole of the arachnoid may be deeply pigmented. Primary melanomata of the arachnoid have been described, but before this diagnosis is made great care should be taken to exclude the possibility of an inconspicuous skin melanoma.

The amount of pigment is variable, not only in the primary growth but also in the secondary deposits; some tumours may be quite pale, others of a deep black colour. The amount of pigment present bears no relationship to the degree of malignancy and many tumours arise which have all the histological characters of a melanoma in which no melanin can be demonstrated. At times the tumour cells may degenerate completely, with the result that cysts filled with a black fluid are formed. So much pigment may be liberated with or without degeneration of the tumour that it may appear in the blood and the urine.

THE ENDOTHELIOMATA

In entering upon a description of the tumours derived from endothelium we are confronted with quite exceptional difficulties, for in respect to no other class of neoplasms is there so wide a divergence of opinion.

There are some pathologists who make a diagnosis of endothelioma in only the rarest cases, and then more as a concession to existing prejudices than from a sense of conviction; in the view of others the endotheliomata occupy a large and important place, and include many tumours which more conservative observers would describe unhesitatingly as carcinomata. Even among the extremists of the latter school there seems to be some uncertainty exactly as to what constitutes an endothelioma, and there is no authoritative pronouncement on the subject to which the student can refer.

In Adami's system of classification the endotheliomata come under the heading of **transitional lepidomata**; they are regarded as being developed from " rind " tissues which are themselves derived from the primitive " pulp." In their growth, therefore, they may assume lepidic, or epithelial, characters, or, if of a higher grade of malignancy, they may revert back to the more primitive sarcomatous type of cell. This

behaviour on the part of the vegetative endothelial cell necessarily militates against complete uniformity in our interpretations of different histological pictures, and may explain to some extent the confusion that surrounds these tumours; but much of the trouble seems to result from fundamental differences in our conceptions of what constitutes a carcinoma, and of the potentialities and limitations of malignant cells in general.

The innocent endothelial tumours, the histiomata, present few difficulties, and their nature is seldom in doubt. It is in the malignant forms, the cytomata, that confusion arises, because the standards by which the neoplastic endothelial cell can be recognised are not clearly defined.

According to most authorities the points of importance in the diagnosis would seem to be the following: the close relationship of the cells to blood vessels; their whorled arrangement, and the absence of any suggestion of a glandular or acinous formation; the presence of giant cells; the tendency on the part of groups of cells to form central lumina which often contain blood; the formation of regular columns of cells two or three layers thick, or of elongated tubules; and the comparative innocence of the tumours.

It is necessary to examine certain of these properties closely in order to determine whether they can readily be considered distinctive of any particular form of tumour.

Taking first the close relationship of the tumour cells to blood vessels, we find that this occurs in many neoplasms. It is very common in the sarcomata, and may often be seen in the carcinomata; nothing for example, could be closer than the assocation between the parenchyma and the supporting capillaries of the hypernephroma. Mere grouping of the cells around vessels, then, cannot be considered a peculiar property of the endotheliomata; it is necessary to demonstrate a much more intimate connection—the direct origin of the cells from endothelium, or an attempt on their part to exercise their normal function of lining channels which could contain circulating blood or lymph. In the ordinary course of events the normal structure of the tissues must be completely obscured by proliferation of the tumour cells, and in growths of any but microscopic size the site of origin must be indistinguishable We could not expect to be able to recognise the actual "malignant degeneration" of the endothelial cells of pre-existing vessels except in very rare instances and by extreme good fortune. The close association of tumour cells with blood vessels which has been brought forward as indicating their endothelial origin might just as

well be explained by permeation within the lumen of the vessel or in the perivascular lymphatics, or by the survival of tumour cells which are adjacent to blood vessels and are therefore less susceptible to the degenerative changes of malnutrition. We need not consider the obvious fallacy of hæmorrhage into a tumour of loose texture, for this should not demand serious discussion.

With regard to the formation of lumina in general, it is necessary to realise that this process is quite common in the simple carcinomata. Before such spaces can be considered as being in any way indicative of a growth of endothelial cells, it must be certain that they are not simply the result of degenerative changes; therefore, the cells lining the lumina must be as healthy and well formed as those at the periphery.

Lack of differentiation of the tumour cells, and failure on their part to form tubules or acini, must not be considered as negativing the possibility of the carcinomatous nature of a neoplasm. In the carcinoma simplex there is no hint of the glandular origin of the tumour, nevertheless, as we have seen, all stages can be traced between this form of cancer and the adenocarcinoma. Similarly, the cells of a typical squamous carcinoma may in certain areas lose all differentiation; there may be no prickle cells and no keratinisation Again, the cells of a carcinoma simplex, when growing in solid acini, may exhibit appearances strongly suggestive of "whorl formation"; and the assumption by the cells of a squamous carcinoma of a spindle form is well recognised. It seems, then, that unless the whorl formation is very distinct, it is unjustifiable to place too great a reliance upon what may be, after all, quite a secondary phenomenon.

A study of inflammatory lesions teaches us that the mesenchymal cells are peculiarly liable to form giant cells, and because of this some pathologists are inclined to regard the presence of giant cells in a tumour as strong evidence of its endotheliomatous origin, especially in combination with a marked variation in the size of the parenchyma cells. However, the histiocytic mesenchymal cell which most commonly forms giant cells bears little relationship to the true vascular endothelial cell which seldom undergoes this change. Moreover, it is in a rapidly growing carcinoma that we might be prepared for just such features as irregularity in the size of the cells, abnormal forms of cell division with the production of giant cells, and absence of any glandular structure; so that this line of argument is not very convincing.

Enough has been said to make it clear that the atypical endothelioma can scarcely be regarded as having an established position, and it is, perhaps, permissible to add that a serious obstacle in the way of their

universal recognition exists in the natural reaction which has followed the indiscriminate use of the term in the last few years. There has been far too great a tendency to name any unrecognised or anomalous tumour an endothelioma, and though such a course may have its immediate advantages, it has helped not a little to obscure an already sufficiently difficult subject.

It will be convenient for our purpose to divide the Endotheliomata into three groups:

I. Vascular endotheliomata.
II. Lymphatic endotheliomata.
III. Endotheliomata growing in connection with serous membranes (mesotheliomata).

I. Vascular Endotheliomata. Tumour growth of the lining cells of blood vessels may be accompanied by a proportional proliferation of simple connective tissue, or it may not. In the former case the resulting tumour will be a histioma, in the latter a cytoma. It is doubtful whether the majority of the vascular histiomata, or angeiomata, should be included among the blastomata at all; they are rather in the nature of dilatations and elongations of pre-existing vessels than true new formations. It is usual, however, to recognise two main types, the capillary angeioma, and the cavernous angeioma.

The **capillary hæmangeioma** (telangiectasis) is a tumour composed of groups of capillary vessels containing fluid blood. The capillaries are of unequal size, and their walls are extremely delicate, consisting of little more than endothelium supported by a scanty stroma of connective tissue. Many of these growths are congenital, and this is notably so in the skin, where they form the familiar vascular nævus, or birth-mark. Apart from the skin, they are also found in the subcutaneous tissue and in muscle. Of the greatest importance is the capillary angeioma of the pelvis of the kidney, for although it is quite small it may give rise to fatal hæmorrhage. Similar telangiectases of mucous membranes may occur in other situations.

The **cavernous hæmangeioma** is found chiefly in the liver, where it is the commonest type of new growth. The tumours may attain to a considerable size and are frequently multiple. Like the capillary angeioma, this form consists of a collection of blood-containing spaces, but it differs in that the capillary walls are thick and are composed of fairly dense fibrous tissue (Fig. 109).

In the case of the vascular nævus it is patent that we are dealing with a congenital malformation rather than a blastoma, and though

the other angeiomata may not reveal their blastomatoid nature so obviously, we should exercise considerable caution before placing any one of them among the true neoplasms.

Fig. 109. Microscopic section of a cavernous angeioma of the liver showing irregular trabeculæ of fibrous tissue enclosing spaces with an imperfect endothelial lining. [illegible] mm. apochrom. Comp. oc. [illegible] Tube-length [illegible]

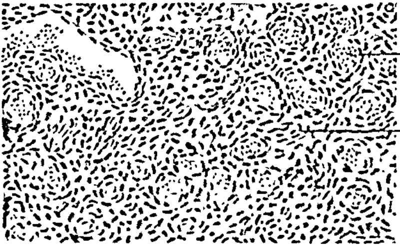

Fig. [illegible] M[illegible]

Hæmangeioma Simplex. These tumours occur as a rule in the subcutaneous tissues, where they form small lobulated growths. They are composed essentially of large endothelial cells, which are arranged in several layers around blood-containing tubules (Fig. 110);

sometimes very few tubules are present, and the cells form solid columns. There is only the smallest amount of connective tissue uniting the separate lobules.

The hæmangeioma simplex is an innocent tumour, though it is said to give rise occasionally to metastases. It is never definitely localised or encapsuled, however, but has remarkable powers of infiltration ; its margin is ill-defined, and it extends widely in the subcutaneous tissues or among adjacent muscle bundles.

The hæmangeioma simplex has many of the characteristics of a true

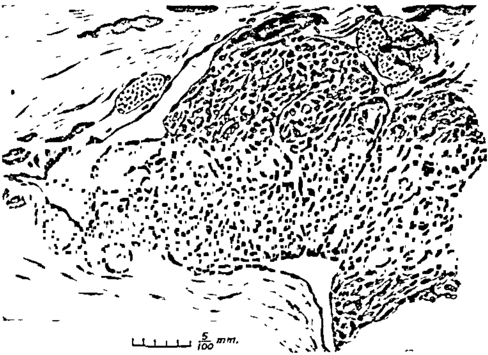

FIG 111 Section of a sinus in the tumour illustrated in Fig 112 showing the "solid" type of endothelial growth seen also in Fig 113

neoplasm rather than a blastomatoid process, but the fact that its tubules contain circulating blood raises a very interesting point, for it implies a physiological connection with the neighbouring healthy vessels. It is quite possible for such a connection to exist between an innocent blastoma and the parent tissue from which it took origin, but there are certain tumours which, while still retaining their association with healthy vessels, present all the histological characters of malignancy. It is difficult to understand how this can occur. The only reasonable explanation is that the tumour mass is constantly being added to by the progressive malignant transformation of the cells of healthy capillaries in the neighbourhood; but this conception is

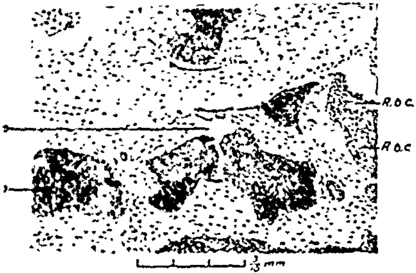

FIG. 112. Section of a malignant haemendothelioma of the muscles of the back. The tumour consists of solid areas of growth having the structure of a spindle-celled sarcoma (1). These are associated with large blood-containing sinuses (2). Compare with Figs. 113-115.

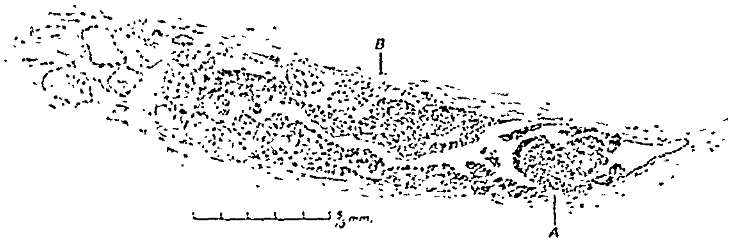

FIG. 113. A large sinus in the tumour illustrated in Fig. 112. It is filled with papillary ingrowths of the lining endothelium. Some of these papillomata are solid (A), but others consist simply of coiled capillaries (B).

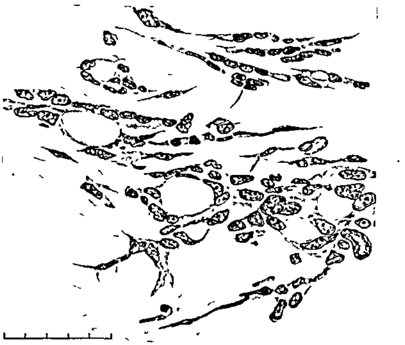

FIG 116. Section from the periphery of the tumour (Fig 114) showing the vasoformative type of cell The tumour cells grow as branching, vacuolated syncytia

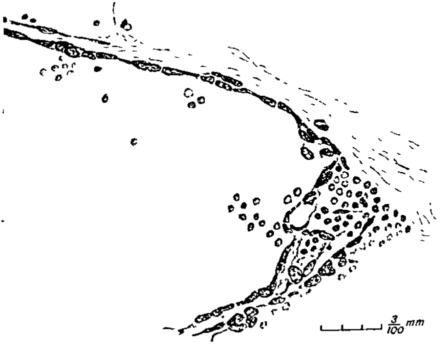

FIG 117 The cells of the tumour are forming the endothelial lining of a blood space

in size and shape so that no typical forms exist, but they present, nevertheless, characteristics which place their origin beyond doubt. At the growing margin branching syncytial forms occur which bear a striking resemblance to vasoformative cells (Fig. 116), and when growing in looser tissues these syncytia may be drawn out as a flattened lining to a blood-containing space, that is to say, they form an endothelium (Fig 117) And however variable the tumour cells may be in most respects, one very constant feature is the occurrence in the

Fig 118 Section of a solid area of the growth illustrated in Fig 114 Vacuoles appear in the cells, and these by their coalescence form large spaces

cytoplasm of vacuoles which do not contain fat but are apparently the result of a simple hydropic degeneration. Figs. 118 and 119 show how the large bloodspaces of the tumour are formed from solid cell masses by the development and coalescence of these vacuoles. A similar process occurs normally in the formation of new vessels, whether they are derived from budding of the endothelium of pre-existing capillaries, or whether they arise from the growth and fusion of the vasoformative cells of the mesoblast In the tumour, the large spaces result from a degenerative process in the essential cells of the neoplasm, a process which has its counterpart in the physiology of the normal angeioblast, though it is quite uncontrolled in the malignant cell. Tumours of this

type have no physiological connection with the vascular system of the host ; there is no true circulation of blood within them, but the spaces merely contain blood because it is effused into the tissues from capillaries of the stroma which have been infiltrated and ruptured by the growth of the tumour cells.

It is from the study of such tumours as this that one may hope to establish the standards by which the neoplastic endothelial cell can be recognised The negative properties of a cell cannot demonstrate its origin, and it is only when the cells of a neoplasm present positive evidence of their endothelial nature that we are justified in calling the tumour an endothelioma. It is not claimed, of course, that the endothelial cell has no other functions than the formation of capillaries or endothelia ; it plays an important part in many inflammatory reactions and frequently breaks loose to become a free wandering cell. But in these circumstances it loses its distinctive characters and can only be recognised with difficulty. Similarly it is quite possible that many of the anomalous tumours met with from time to time may consist of atypical neoplastic endothelial cells. But since this cannot, at present, be proved, there is no justification for labelling such tumours as endotheliomata.[1]

FIG 119 A more advanced degree of the cell vacuolation seen in Figs 116 and 118 By the fusion of neighbouring vacuoles large spaces have formed into which blood has oozed

In addition to the typical malignant hæmendothelioma, it is necessary to consider the unusual type in which the neoplastic tissue is multicentric in origin All these growths are rare, but the best known is **Kaposi's multiple hæmorrhagic sarcoma.** This is characterised by a number of nodular hæmorrhagic lesions in the limbs which spread to involve the whole skin surface. In the early stages the histological picture is reminiscent of vascular granulation tissue, but in the late

[1] See also Kettle, *Proc Royal Soc Med.*, 1918, **11**, 19, and Kettle and Ross, *Lancet*, 1921, 1, 1012

stages the angeiomatous elements become more prominent so that it more closely resembles a hæmendothelioma though the lesions remain in the borderland between blastomatoid proliferations and true neoplasms; in some cases the stromal change is more marked so that the appearance is that of a vascular fibrosarcoma. The lesions are not limited to the skin, but in most cases examined post-mortem there are scattered angeiomatoid areas throughout the body.[1]

Multicentric hæmendotheliomata have also been described arising in the liver, spleen and bone marrow and in some of these there has been evidence of hæmopoiesis in addition to angeioblastic formation. These tumours are regarded as being derived from primitive sinus lining mesenchymal cells which in the embryo have this dual potentiality, though there is no evidence that adult type vascular endothelium has any hæmopoietic competence.[2]

Perithelioma was a tumour described by some of the older pathologists in which tumour cells were arranged around blood vessels as a cuff and their origin was variously attributed to vascular or lymphatic endothelium. Although it is true that tumours are often found in which cells are arranged in this manner it is doubtful if they represent a distinct tumour type. In the majority of cases they are variants due either to necrosis of cells furthest from and survival of those closest to their blood supply, or to a perivascular scirrhus stromal reaction or to a spread of the tumour in the perivascular lymphatics. A peritheliomatous formation may be found in a large variety of poorly differentiated carcinomas or sarcomas. A perithelial type of growth is a good descriptive term, but perithelioma is unjustifiable as a diagnosis

II. **Lymphatic Endotheliomata.** It is possible to distinguish similar progressive changes in the lymphatic vessels and their lining cells, but, in the absence of blood, their recognition may be a matter of difficulty.

The **simple lymphangiectasis**, corresponding to the vascular nævus, consists of collections of dilated lymph vessels, and is usually situated in the skin of the face and neck *It is congenital in nature. Closely* associated with this condition is the **cystic lymphangiectasis.** Here, combined with an active secretion into the lumina of the capillaries, there is obstruction to the outflow of the fluid, with a consequent dilatation of the tubules. The best-known example of this process is seen in the **cystic hygroma** of the neck. This is composed of a collection

[1] Choisser and Ramsey, *Am J Path*, 1939, **15**, 155

[2] These tumours have been well discussed by Willis "The Spread of Tumours in the Human Body" London, Churchill, 1934, p 148, and Ogilvie and Mackenzie, *J. Path and Bact*, 1936, **43**, 143.

of large spaces containing clear lymph, and bounded by fibrous tissue lined by endothelium.

The **cavernous lymphangeioma** has a structure comparable with that of the cavernous angeioma (Fig. 120). It is the underlying process in such congenital conditions as diffuse enlargement of the lip and tongue, known as macrocheilia and macroglossia respectively.

True lymphatic blastomata occur in the subcutaneous tissues and muscles, but they are rare. In some of them the growth is mostly solid, but in others a multitude of large spaces are formed, lined by a swollen

FIG 120 Microscopic section of a cavernous lymphangeioma of the back The tumour consists of a collection of thick-walled spaces lined by proliferated endothelial cells
Obj 16 mm apochrom. Comp oc. 6 Tube length, 160 mm

endothelium. Sometimes the tumour consists of innumerable minute tubules lined by endothelial cells which are only slightly larger than the normal (Fig. 121).

III. ***Endotheliomata growing in Connection with Serous Membranes.*** Golgi introduced the term endothelioma for the dural tumour which is now generally known as a meningeioma (p. 171) Although the vascular and lymphatic tumours are universally accepted as endotheliomata, there is still some dispute in regard to the tumours arising from the lining cells of the serous cavities. Apart from the membranes of the brain and cord which have already been considered these included the pleural, pericardial and peritoneal cavities, the tunica vaginalis and the synovial lining of joints and tendons. The synovial tumours for all that they are derived from fibroblasts, have histological characters which fully justify their inclusion as endotheliomata, yet

it will be more convenient to consider them in the section on special pathology (p. 214). With regard to tumours arising in connection with

FIG. 121. Microscopic section of a lymphendothelioma of muscle. Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

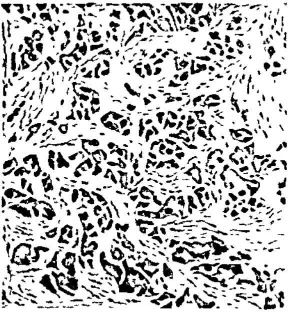

FIG. 122. Microscopic section of an endothelioma of the pleura. The tumour cells vary considerably in size and shape, and are loosely grouped together in irregular acini.
Obj. 8 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

the large serous cavities the problem is more difficult. Undoubtedly tumours do arise from these situations, but they are rare and the majority of pleural or peritoneal endotheliomata are in reality examples of serosal spread from an inconspicuous primary carcinoma of the bronchus, stomach, pancreas or gall bladder. In well authenticated examples of primary serosal endotheliomata (mesotheliomata) the tumour cells are commonly polygonal shaped exhibiting an irregular acinous structure in a fibrous stroma, but before this diagnosis is put forward a most thorough investigation to exclude the possibility of metastatic carcinoma must be made.

Similarly endotheliomata undoubtedly arise in lymphoid tissue. They too are rare, and many that have been so described have been either reticulo-sarcomata (p. 108) or hyperplastic proliferations of lymphoreticular tissue (the lipoidosis generally known as Gaucher's disease was originally described as an endothelioma of the spleen) and in the majority of cases they prove to be a diffuse infiltration with an anaplastic carcinoma.

The ovarian "endothelioma" or Krukenberg's tumour is a diffuse secondary carcinoma and the endothelioma of salivary glands is a low grade carcinoma. The tumour known as an endothelial myeloma or Ewing's tumour of bone will be considered under bone (p. 220).

THE TERATOMATA

So far we have been dealing with the autochthonous blastomas, tumours derived from unipotential cells native to the host or individual bearing them.

We have now to consider a group of neoplasms of a more complex *structure and origin.*

A teratoma is a tumour arising from a cell or group of cells capable of producing cells or tissues representative of all three primitive layers of the blastoderm.

The commonest and most important examples of this group are seen in the ovary and the testicle. Extragenital teratomata arise anywhere in the mid line of the body from the region of the basisphenoid to the coccyx. Thus they occur in the thorax, abdomen, and cranium, and also grow from the lower part of the vertebral column, where they form the well-known **sacrococcygeal tumour.** They may be innocent or malignant, and their structure is extremely complicated. With the rise of thoracic surgery the importance of teratomata of the mediastinum has been emphasised and their unsuspected frequency revealed.

Ovarian Teratomata. These tumours occur usually in early adult life and may be present in quite young children. They are often bilateral, and they are rarely multiple in the same organ.

Two forms are to be distinguished, the cystic and the solid, the former, the familiar "dermoid cyst," being by far the commoner.

The dermoid cyst may be uni- or multi-locular, and may attain to a considerable size. It is filled with a sebaceous material in which are

FIG. 123 Sacrococcygeal tumour.

to be found bundles or long strands of hair. The hair may be free in the cavity, but is more often attached to a nodular projection, on the inner surface of the wall. Teeth are sometimes inserted into the wall around the base of this nodule.

The cyst wall is lined by squamous epithelium beneath which are many sweat and sebaceous glands (Fig 124). Other tissues, cartilage, bone, muscle, and glandular and nervous elements are also frequently to be found (Fig. 125), and they may be so arranged as to resemble the structure of organs such as the trachea or the intestine. This is

particularly the case in the nodular protuberance or "head." Occasionally one tissue element in an ovarian teratoma is found to have undergone malignant change and may produce metastases although the other elements have remained slow-growing and benign; thus a squamous cell carcinoma is not infrequently found and other carcinomata have been described. *In this way a blastoma arises in a teratoma;* an example of teratogenous blastoma.

The solid ovarian teratoma is a rare tumour, and usually a malignant one. It exhibits the same mixture of tissues and cells as the cystic

FIG 124 Microscopic section of the wall of a dermoid cyst of the ovary, showing the lining of squamous epithelium (1) beneath which are many sebaceous glands (2)

Obj 16 mm. apochrom. Comp. oc 4. Tube length, 160 mm.

variety, though they are often less well differentiated. This tumour tends to disseminate, and the metastases may be of the mixed cell type or may consist of cells of one order.

Testicular Teratoma. These, on the other hand, are nearly always solid tumours; a simple dermoid cyst of the testicle is an extreme rarity. They occur most commonly in young adults, and form firm rounded tumours which, on section, present a variable picture. In the commonest form the growth consists of a dense, somewhat pale tissue in which are innumerable tiny cysts. Sometimes the cysts are larger, giving a spongy appearance to the growth, or there may be a

Fig. 125. Microscopic section of a teratoma of the ovary showing stratified epithelium (1), cartilage (2), fat (3), osteoid tissue (4) bundles of smooth muscle fibres (5), and mucous and serous glands (6)

Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

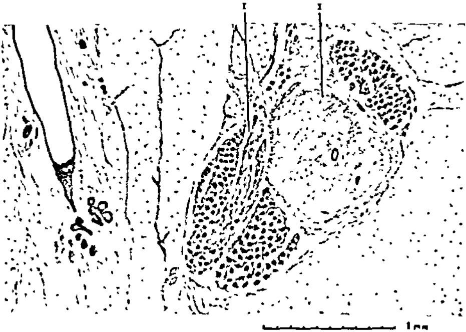

Fig. 126. A teratoma of the ovary showing a mass of glial tissue (1) containing a central canal lined by columnar epithelium and groups of ganglion cells with nerve fibres. It suggests an attempt to form a spinal cord with ganglia.

disproportionate dilatation of one or more of them. Some tumours are more solid, containing few macroscopic spaces, but showing *hæmorrhage, œdema, and other degenerative changes.* As a rule, however, the general structure is indicated in the name, **fibrocystic disease**, by which this tumour was formerly known (Fig. 176, p. 276).

Microscopically, a very usual structure is that of a collection of tubules, lined by columnar epithelium, and surrounded or separated by bundles of smooth muscle fibres, the whole lying in a loose fibrous

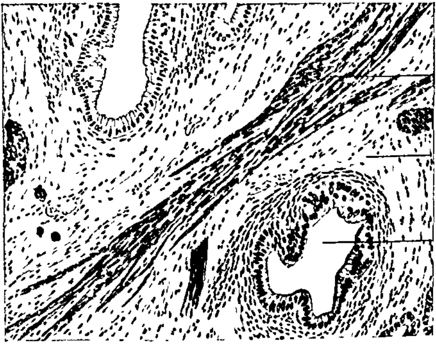

FIG. 127 *Microscopic section of a teratoma of the testicle* (1) Tubule lined by columnar epithelium and surrounded by condensed stroma; (2) loose connective tissue, (3) bundles of smooth muscle fibres

Obj 8 mm apochrom Comp. oc. 4. Tube length, 160 mm.

tissue stroma (Fig. 127). Islands of squamous epithelium, hairs, and masses of cartilage are often present as well; indeed, by a careful examination, derivatives of all three of the primary layers of the blastoderm can generally be made out. In many tumours cell differentiation may be rudimentary and the greater part of the growth have the structure of a carcinoma composed of undifferentiated epithelial cells of an embryonic type.

Both innocent and malignant testicular teratoma are described, but it is doubtful if this distinction is justifiable. In some tumours the constituents may be of a more immature type than in others, and these

tumours are usually highly malignant. But dissemination and a fairly rapid growth may be associated with histologically innocent tumours in which the cells are well differentiated. Again, the histology of individual tumours may vary in different parts, so it is wise to regard every testicular teratoma as potentially malignant. Dissemination may be delayed or it may occur quite early; and metastases may be mixed or limited to one type of cell.

Since the cells lining the seminiferous tubules are potentially toti-potent it might well be argued that any tumours arising from them would be teratomata. Why some tumours exercise their varied potentiality and others do not is not clear.

The origin of teratomata in general is a matter of speculation. In the testicle and ovary there are cells with potentiality sufficiently great to account for them, but elsewhere some more obscure cause must operate. All that can be suggested so far is that anywhere in the midline and at the anterior and posterior growing points toti-potent cells may become segregated at an early stage in development. There is little to support the old view that a teratoma is some sort of inclusion twin. Both Nicholson and Willis have advanced convincing arguments in opposition to this. Differentiation is the expression of a physiological principle of growth in both embryo and teratoma, but teratomata possess none of the characters essential for independent existence. In the embryo special organs are developed by a sequence of special reactions and depend on the interaction of structures which were primarily independent. In the teratomata there is no evidence of such reaction and interaction. Apart from some of the tissues having a recognisable form such as skin or intestine there is no evidence that one tissue or organ has any influence on another. In teratomata the potentiality for differentiation is manifest, but there is no indication of integration and organisation.

It is clear that a knowledge of determinative embryology is essential for a full appreciation of teratoma formation. It seems probable, as Willis has suggested, that a teratoma represents an area of undifferentiated tissue which in some way has escaped from the co-ordinating influence of the main axial organiser or evocator and that the subsequent nonaxial differentiation is the outcome of a persistent competence to respond to lower grade evocators released by the tissues themselves. Needham [1] has suggested that the sacro-coccygeal teratoma is exactly comparable with the phenomenon of exogastrulation.

[1] Needham, J., *Proc. Roy. Soc. Med*, 1935, 29, 1577.

Teratoblastomata

This group includes the "mixed" tumours that are found in several situations, but chiefly in the kidney and the female genital organs. These tumours occur in their most characteristic form in the kidney, and have been described under many different names—*carcinoma sarcomatodes, sarcoma of infancy, adenosarcoma,* and *rhabdomyosarcoma.*

The majority of renal teratoblastomata occur in infancy or before the end of the second year. They form large rounded tumours growing in the kidney with the cortex spread out over them in a thin layer. They are of a moderately firm consistence, and of a whitish appearance.

Fig. 128. Microscopic section of a teratoblastoma of the kidney. (1) Loose œdematous stroma; (2) groups of indifferent sarcomatous cells enclosing (3) epithelial tubules.
Obj. 8 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

Sometimes they exhibit areas of hæmorrhage, and there is nearly always a considerable degree of degeneration. Their *microscopic* structure is highly characteristic. The main mass of the tumour is composed of small rounded or oval cells of a distinctly sarcomatous type, lying in a loose œdematous or myxomatous connective tissue matrix. Intimately mingled with these cells are tubules lined by columnar cells, and these epithelial elements may be present in great numbers (Fig. 128).

More rarely, islands of cartilage and smooth and striated muscle fibres can be distinguished, but there is never any orderly grouping or arrangement of the different constituents such as is seen in the true teratomata. The tumours are highly malignant, infiltrating locally and forming metastases.

Similar tumours arise in the uterus, vagina and bladder of children and adults, but the so-called mixed tumours of the salivary glands are in reality epithelial neoplasms with an unusual stromal reaction.

With regard to the origin of the renal teratoblastomata, the commonly accepted theory is that of Wilms. He suggested that these tumours arise from mesoblastic tissue derived from the myotome which gives rise to the lateral cell mass, the kidney anlage and connective tissue elements. Masson[1] in a paper illustrated by beautiful photomicrographs has confirmed that these tumours consist of mesenchyme and renal epithelium He has, however, stressed the presence of nerve fibres. He says " They are composed of the renal glandular elements, mesenchymatous elements and striated muscle . . . also of neuro-epithelial and nervous elements."

He argues that neural tissue is the earliest of the tissues and therefore the origin of the tumour. " This leads to the conception that in the normal embryo, certain striated muscles and the nephrogenic tissue have for their origin not the mesoderm (mesendoderm), but the mesoectoderm of the neural crests." Histological observation is limited, and although a great deal has been and has yet to be learnt by the comparison of sections from series of lesions it is fatally easy to assume processes which cannot be seen.

If Masson was right he has suggested a new origin for the kidney and confirmed the older view that these tumours arise from cells capable of differentiating to form connective tissues on the one hand and well differentiated epithelium on the other.

Chorioncarcinoma (Heterochthonous Blastoma)

This tumour is of very great interest, possessing as it does features which single it out from all other neoplasms.

Of all the tissues of the body none so nearly mimic the infiltration of a tumour as the trophoblast and the chorionic villi. It is their normal function to burrow into the uterus and to communicate with the maternal blood sinuses. Under normal conditions following the delivery of the fœtus this tissue disappears and even if chorionic villi or pieces of them get washed away in the blood stream and reach the lung they fail to survive there.

Chorioncarcinoma arises from the trophoblast of the fœtus. Although it is not an integral part of the fœtus it does normally develop from the developing fertilised ovum, and is an essential part of the developing embryo. It is to this extent an example of a tumour

[1] *Am. J. Canc*, 1938, 33, 1.

developing in the tissues of one individual infiltrating the tissues of another. It may occur during the course of, or after a normal delivery or abortion, but in about 80 per cent. of cases it is preceded by a *hydatidiform mole*.

It is noteworthy that the incidence of the tumours rises in proportion to the number of previous pregnancies; the mother of five children is more likely to suffer than a woman who has borne but one or two.

The primary growth may be situated in the uterus where it forms a polypoid fleshy mass, in the vagina, in the Fallopian tube, or in the ovary; it is an extremely hæmorrhagic growth, consisting mostly of blood clot enclosed in a thin irregular shell of paler tumour tissue. Dissemination usually takes place with great rapidity by the blood stream; the earlier and more numerous deposits are found in the lung and the liver, but any other part of the body may be affected.

The chorioncarcinoma of pregnancy is itself an uncommon phenomenon; still rarer are the instances of its development apart from childbearing. Cases have been recorded, however, in which it has appeared in teratomata of the testicle, the ovary, and the thorax. The importance of these observations will be referred to later.

The chorioncarcinoma is one of the most fatal of all malignant growths, but some most remarkable examples have been established of spontaneous disappearance of the tumours and complete recovery.

The *histology* of the tumour is quite distinctive, though it is often obscured by hæmorrhages and degenerative changes.

Its cells are of two main types, corresponding as we now know to the Langhan's cells and the syncytium of the chorionic villi (Fig. 129).

The Langhan's cells are polygonal or cuboidal in shape, and have a clear vesicular cytoplasm; their nuclei are relatively large, possessing a well-marked chromatin network and nucleolus, they multiply by indirect division.

The syncytial elements consist of large masses of dense protoplasm containing several very deeply staining oval nuclei. Frequently the protoplasm is drawn out into long narrow processes resembling endothelium. In the larger masses there may be vacuoles filled with fluid blood

The two constituents may be mingled together, but more commonly the syncytium lies at the periphery of the closely packed masses of Langhan's cells. Recognisable chorionic villi are often found, but their stroma is always vesiculated.

The tumour has no stroma of its own, and has therefore no true structure, though it may be moulded into an irregular form from its

mode of growth along the vascular channels of the normal tissues. It possesses no blood vessels, but derives a precarious nourishment from the circulating blood of the host; for this reason its cells are unusually liable to undergo degenerative changes. It grows freely in blood vessels, distending and eroding them, and this peculiarity offers an obvious explanation of its rapid dissemination and its universally hæmorrhagic nature.

The character of the chorioncarcinoma is so well established that it is not easy to appreciate how doubts could have been entertained

FIG. [illegible].—Microscopic section of a chorioncarcinoma of the [illegible]. (1) Muscular tissue of the uterine wall. (2) [illegible] (3) [illegible] Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, [illegible].

as to its origin. Nevertheless, for some years the [illegible] acute controversy. Even when its association with pregnancy was recognised it was supposed to be derived from the [illegible] name, deciduoma malignum, implies.

As a matter of fact, in no other malignant growth [illegible] clearly the stages in the transition from the normal. [illegible] villus to the typical chorioncarcinoma the chain is [illegible] the simple hydatidiform mole, the perforating or malignant hydatidiform mole, and the chorioncarcinoma in which [illegible] though atypical, chorionic vill[illegible]. The [illegible] complete by the recognition [illegible] in such [illegible].

tumours as the testicular and other teratomata to which reference has already been made.

Further, these tumours produce an active gonadotropic hormone greater in amount than that found in normal pregnancy, it is excreted

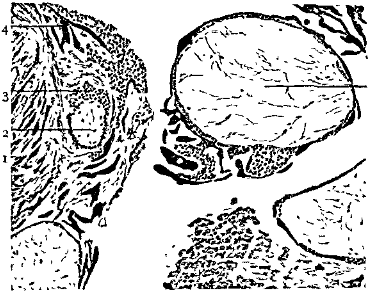

FIG 130. Microscopic section of chorionepithelioma of the uterus.
(1) Uterine wall, (2) chorionic villi; (3) Langhan's cells, (4) syncytium
Obj 16 mm apochrom Comp oc. 4 Tube length, 160 mm

in the urine and its assay by means of animal tests is a most valuable aid in diagnosis.

When true chorioncarcinoma is found either in the female apart from pregnancy or in the male it is always associated with a teratoma. In some few cases the teratoma may be destroyed by the overgrowth of chorioncarcinoma, but in most cases it will be found if a thorough search is made. Not only is the histological appearance typical in these cases, but they also provide evidence in the urine of their hormonal activity.

PART III

THE SPECIAL PATHOLOGY OF TUMOURS

THE SKIN AND SUBCUTANEOUS TISSUES

By virtue of their accessibility, the tumours of the skin form eminently suitable objects for clinical and pathological study, while from their variety they offer a rich field for investigation. The subject is a difficult one, for there also occur in the skin a number of hyperplastic processes and congenital formations which closely simulate true blastomata; and, added to these natural sources of confusion, we have others arising from a tendency on the part of some authors to an exaggeration of minor differences in growths of the same character.

Though to the dermatologist such fine discriminations have, no doubt, a clinical significance, to the general pathologist they seem a regrettable elaboration of an already complex subject.

Innocent Tumours. **Fibromata** are not very common, though blastomatoid overgrowths of fibrous tissue, both localised and diffuse, are not infrequently seen; such a well-known condition as **keloid** may be quoted as an example of blastomatoid fibromatosis. The true fibromata form hard rounded tumours, often multiple, and occasionally of some considerable size.

Lipomata are common in the subcutaneous tissues; they form smooth lobulated tumours of a somewhat darker colour than the surrounding fat. Sometimes the tumours contain so much fibrous tissue as to warrant their being named fibrolipomata.

Leiomyomata are occasionally seen as small tumours, often multiple, arising from the arrectores pilorum, or the walls of vessels. They are often extremely painful although nerve elements cannot be demonstrated in them.[1]

Schwannomata are not uncommon and **neurofibromata** are found in association with von Recklinghausen's disease.

Myxomata are rare and are usually myxo-lipomata often of an embryonic type.

Xanthomata (p. 80) are frequent in the skin and are classified by dermatologists into numerous types according to their situation and the general clinical condition[2]; sometimes the fibrous stroma may

[1] Stout, A. P., *Am. J. Canc.*, 1937, 29, 435.
[2] Thannhauser, S. J. and Christian, H. A., *Lipidoses*, London, 1940.

be so marked as to render the xanthoma cells inconspicuous unless frozen sections are stained for fat.

Histiocytomata have been described in the dermis, but it is doubtful whether they should be regarded as true neoplasms.[1] They form ill-defined whitish-brown subcutaneous nodules which are frequently ulcerated; microscopically they consist of closely set spindle-shaped histiocytes and multinucleate giant cells often containing altered blood pigments and lying in a moderately fibrotic stroma.

Blastomatoid involvement of the dermis is frequent in disorders of the lymphoreticular tissue varying from a leukotic infiltration to the complex cellular proliferation known as mycosis fungoides There is much obscurity in the exact relationship between these conditions and analogous states found in the lymph nodes, and spleen.

Hæmangeiomata and **lymphangeiomata** are of frequent occurrence in the skin and subcutaneous tissue; as has already been pointed out (p. 186), the majority of them are congenital blastomatoid processes, and not true tumours. In some cases there is a simultaneous hyperplasia of the fibrous tissue, resulting in the production of the **fibro-angeioma.**

A peculiar vascular neoplasm is the **glomus tumour** or angeioneuromyoma. These are blastomatous formations of peculiar arteriovenous anastomoses which occur in the deep dermis, particularly in the fingers. They form small tumours seldom more than a centimetre in diameter often forming a bluish dimple near the nail-bed and are exquisitely tender and the pain may radiate up the limb. Microscopically they are commonly encapsulated and formed of blood spaces lined by flattened endothelial cells which are surrounded by a network of reticulin fibres between which lie the glomus cells—large cuboidal cells with a prominent nucleus and a pale somewhat vacuolated cytoplasm They are believed to be modified smooth muscle cells and similar "epithelioid" cells are to be found in the wall of the normal glomus. The tumour commonly shows numerous normal vessels in the vicinity and is richly supplied with nerve fibres Masson [2] who gave the first clear description of these tumours, recognises various types according to the degree of vascularity and connective tissue proliferation. They are benign, but local recurrences have been described.

Solid and cystic epithelial tumours may grow from the surface

[1] Gross, R E, and Wolbach, S. B, *Amer. J Path*, 1943, 19, 533
[2] Masson, P, *Bull de l'assoc. Franc. de derm. et Syph* 1935, 42, 1174, Lendrum, A. C, and Mackey, W. A., *B M.J*, 1939, 2, 676

epithelium, the hair follicles, the sebaceous glands, and the sweat glands, though blastomatoid conditions are more numerous than true blastomata.

An undoubted **papilloma** of the surface epithelium may be seen, though it is not particularly common, but multiple **warts** and **condylomata**, presumably infective in origin, are very frequent.

Molluscum contagiosum is another blastomatoid condition which is certainly an infective process. The tumours are usually multiple, forming small rounded nodules immediately beneath the epidermis; they often show slight umbilication. They consist of solid alveoli of

FIG 131 Molluscum contagiosum. (1) Surface epithelium, (2) masses of epithelium showing (3) molluscum bodies and (4) central keratinisation
Obj 16 mm. apochrom. Comp oc. 4 Tube length, 160 mm

epithelial cells separated from one another by processes of connective tissue, and arranged around a central point. The innermost cells exhibit an anomalous keratinisation, the individual degenerated cells being known as "molluscum bodies," and the centre of the tumours is occupied by soft, completely degenerated cell debris (Fig. 131). The molluscum bodies are cytoplasmic inclusions formed of closely packed elementary bodies (virus).

Simple **adenomata** of the surface epithelium are occasionally seen. They consist of solid masses and trabeculæ of epithelial cells embedded in a fibrous stroma. Sometimes the central cells are keratinised, but more often they undergo necrosis so that pseudocysts are formed, when the tumour is known by the name of **epithelioma adenoides cysticum.**

An ill-named tumour—the **benign calcifying epithelioma**—is uncommon, but may be found in children and young adults. It forms a circumscribed mass in the dermis not connected with epidermis and is encapsulated. The cut surface is firm, whitish with an irregular serpentine pattern. Microscopically it is seen to consist of masses of keratinised epithelium in which are numerous cell nests and there is some calcification. Foreign body giant cells are frequent in the stroma and there may be metaplastic bone formation. It is entirely benign, but its histogenesis is obscure.[1] It is probably a variety of epidermoid cyst.

A simple **epidermoid cyst**, sometimes an "inclusion cyst," may be encountered; it consists of a mass of keratinised material surrounded by a narrow zone of active, healthy epithelial cells. Cystic tumours also arise from the sebaceous and sweat glands. The commonest example is the simple sebaceous cyst (on occasions sebaceous cysts are familial[2]), but multilocular, even papilliferous, cysts may grow from the sweat glands. Both sebaceous and sweat glands are liable to hyperplastic processes, but true adenomata also occur apart from these conditions

In the **sweat gland adenoma** (syringocystadenoma[3]) the structure is usually that of groups of irregular elongated acini, and the appearance is not unlike that of a mammary fibro-adenoma. The epithelium lining the acini is of a low columnar form, and a reversion to squamous cells may take place. On occasions these sweat glands adenomata may show marked stromal degenerative changes so that they resemble the salivary gland tumours (p. 235).

In the axilla adenomata may be found in which the cytoplasm of the epithelial cells is strongly acidophil; these are derived from the apocrine glands

In the **sebaceous gland adenoma** the characteristic cells are grouped together in solid alveoli, which may show a certain amount of central necrosis or calcareous infiltration.

Malignant Tumours.[4] **Sarcomata.** Primary sarcomata of the skin are somewhat rare One of the commonest forms is a slowly growing spindle-celled or fibro-sarcoma; large round-celled sarcomata and polymorphic-celled sarcomata are also met with, and are of a much

[1] Coté, F H, *J Path and Bact*, 1936, **43**, 575.
[2] Ingram J. T, and Oldfield, M C, *B M.J*, 1937, **2**, 960
[3] Shields, Warren, and Warvi, W. N., *Am J. Path.*, 1943, **19**, 441, 591.
[4] A detailed study of malignant skin tumours is to be found in "Cutaneous Cancer and Precancer," by G. M. Mackee and A. C. Cipollaro, New York, *Amer. J. Canc.*, 1937.

higher grade of malignancy. Reticulosarcomata of various types may arise in the dermis; many of these are multicentric and are usually of the lymphoblastic type; they constitute the primary multiple sarcomata of the skin of older writers.

Endotheliomata. The commonest tumour of an endotheliomatous nature occurring in the integument is the **hæmangeioma simplex** (p. 187). This is usually innocent, but it may exhibit an infiltrative growth and become definitely malignant. Comparable tumours derived from lymphatic endothelium may sometimes be encountered. The multiple angeiosarcoma of the skin (kaposis sarcoma) has already been described (p. 192).

Melanomata. These tumours have been dealt with in a previous section (p. 180).

The majority of congenital pigmented moles are, of course, entirely innocent, but they may assume malignant characters and disseminate with appalling rapidity, both by the blood stream and the lymphatic system. Occasionally melanomata may arise independently of congenital moles.

Carcinomata. It is particularly in respect to the malignant epithelial neoplasms of the skin that confusion has resulted from unnecessary elaboration in our classifications. The skin is a highly complex structure, and the numerous carcinomata which grow from the surface epithelium and its derivatives may very naturally exhibit considerable variations from one another. But, unless it is distinctly advantageous from the clinical standpoint, a separation of several distinct forms of tumour growth based on such minor differences would scarcely seem to be justifiable.

The **squamous-celled carcinoma** is a very common tumour of the skin; it may be of the papillary or the infiltrating type, and it is frequently ulcerated. It presents all the distinguishing features of this type of carcinoma (p. 137).

Anomalous histological forms are sometimes met with in which there is an alteration into the adenomatous type. Some of these are obviously derived from sweat glands, but in others it is impossible to distinguish their points of origin. A carcinoma derived from sebaceous glands may reproduce the normal structure of the gland with great fidelity, but it may form a simple alveolar or even a squamous-celled tumour.

The degree of malignancy possessed by different squamous-celled carcinomata is very variable. They all cause local destruction of tissue, but they do not by any means exhibit a constant rapidity of growth,

nor do they all form metastases. For the most part distant metastases are rare, and there is seldom any extension except to the neighbouring glands, but occasionally a case is seen in which dissemination is more widespread.

The importance of external carcinogenic agents as a causative factor is very marked in the carcinomata of the skin. The cancer in the scrotum of sweeps, the cutaneous cancer of paraffin workers, the X-ray and the Kangri cancers are all obvious examples.

Rodent Ulcer (Basal cell carcinoma). This tumour has features which bring it into a class apart from the ordinary squamous-celled carcinoma (p. 139). It occurs as a rule on the face, at the angles of the nose and the eyes, and on the forehead, but extra-facial forms are occasionally seen. Its growth is infiltrative but slow; the facial tumours never form metastases, though these may occur in the extra-facial ones.

Metatypical Carcinoma. These tumours resemble a rodent ulcer clinically, but on microscopic examination are seen to consist either of a basal cell carcinoma in which there are areas of prickle cells and keratinisation or of intermediate type cells which are larger, paler and rounder than basal cells, but show no intercellular bridges or tendency to keratinise. These tumours are much less radio-sensitive than the typical basal cell carcinoma, are liable to metastasise and should be treated as squamous celled carcinoma.

Intra-epidermic Carcinoma (Bowen's disease). In these tumours the neoplastic cells instead of spreading down into the dermis spread along the epidermis between apparently normal cells. The rete pegs are elongated and broadened and lying in these are disorganised collections of poorly differentiated cells often with vacuolation; multinucleate forms may be present and mitotic activity. These intra-epidermic carcinomata may be multiple and are commonly of low-grade malignancy. Paget's disease of the nipple (p. 288) is an intra-epidermic carcinoma of this type.

Xeroderma pigmentosum is a congenital and frequently familial disorder. The exposed areas undergo hyperkeratosis and pigmentation and almost all the patients develop skin cancers at a very early age.

Acanthosis nigricans is a curious condition in which there is hyper-pigmentation and papillary hypertrophy involving the neck and flexion creases of the body. In itself it is harmless, but in over half the cases described internal carcinomata, particularly of the stomach, develop.[1]

[1] Michy, J., *L'Acanthosis Nigricans et ses Rapport avec les tumeurs malignes*, Paris, 1932.

Secondary Tumours. Carcinomata and sarcomata may both give rise to metastases in the skin, though not very often. In mammary carcinomata, however, cutaneous metastases are frequently seen as the result of permeation of the superficial lymphatics. Apart from permeation, the skin may be directly invaded by underlying malignant connective tissue and epithelial tumours, and nodules occasionally form from the lodgment of vascular emboli.

MUSCLES AND FASCIÆ, TENDONS AND BURSÆ

Though new growths of the muscular constituents of various organs are not uncommon, tumours of muscles themselves are rare, and are usually derived from the fasciæ and connective tissue septa. Tumours of tendons and bursæ are even less common.

Innocent Tumours. **Fibromata** are probably the commonest tumours; they may grow from the connective tissue of muscles, and

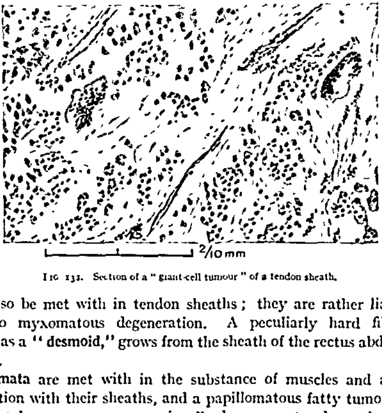

FIG. 131. Section of a "giant-cell tumour" of a tendon sheath.

may also be met with in tendon sheaths; they are rather liable to undergo myxomatous degeneration. A peculiarly hard fibroma, known as a "**desmoid,**" grows from the sheath of the rectus abdominis muscle.

Lipomata are met with in the substance of muscles and also in connection with their sheaths, and a papillomatous fatty tumour, the **lipoma arborescens,** may occasionally be encountered on the inner surface of tendon sheaths.

Hæmangeiomata and **lymphangeiomata** are occasionally seen in

muscles, and a diffuse hæmangeioma simplex may grow in the walls of bursæ; all these formations are probably blastomatoid in nature.

Osteomata are very rare, though metaplastic ossification is not uncommon in both muscles and tendons. A true osteoma, however, may grow in muscles.

Rhabdomyomata have been described, but are extremely uncommon; they are probably congenital tumours, growing from "rests" of embryonic muscle cells.

Giant-cell tumours (p. 88) may be found in tendon sheaths; they are commonly believed to arise in relation to sesamoid bones. They show a marked xanthomatous tendency.

Malignant Tumours.[1] **Sarcomata** are not uncommon in connection with muscles, though they appear to originate in the fascia and connective tissue septa rather than in the muscle fibres themselves. Round- and spindle-celled forms occur, but the commonest type is a slowly growing fibrosarcoma which exhibits a marked tendency to myxomatous degeneration.

Fibrosarcomata are very occasionally found growing from tendons and bursæ.

Liposarcomata may arise in relation to muscle sheaths and have the usual characters of these growths. The debatable "neurogenic fibrosarcomata" have already been discussed (p. 104) and there is no need to add anything to the account of rhabdomyosarcomata which are extremely uncommon.

Synoviomata.[2] Malignant tumours derived from primitive synovial cells may develop in joints and bursæ; they have been described as endotheliomata, but as the synovial cell is a modified fibroblast they are in reality mesodermic.

These tumours are for the most part slow-growing firm tumours, with a tendency to pseudocystic formation and hæmorrhage. Microscopically they vary from poorly differentiated growths formed of sheets of oval cells with little reticulin network to a collagenous fibrosarcoma, but the typical synovioma is composed of alternate zones of spindle cells and more darkly staining cells which tend to form clefts and lumena. In the zones of the spindle cells there is considerable collagen and reticulin formation. These tumours are radioresistant, but metastasise late.

Carcinomata are always secondary.

[1] These have been well reviewed and illustrated in Jönsson, G., *Malignant Tumours of the Skeletal Muscles, Fascial, Joint Capsules, Tendon Sheaths and Serous Bursæ*, Stockholm, 1938.

[2] Berger, L., *Am. J. Canc.*, 1938, **34**, 501

Secondary Tumours. Carcinomata often extend to muscles directly, but seldom produce distant metastases in them. Sarcomata also invade muscles by direct extension, and in some highly malignant round-celled tumours distant dissemination may take place.

THE BONES[1]

Innocent Tumours. Osteomata. In a previous section (p 85) attention has been drawn to the difficulty that exists in distinguishing between the various conditions of bony hyperplasia and the true osseous neoplasms, and there is no necessity to dwell upon the subject again. But it must be clearly understood that when we talk of osteomata, and of other tumours of bones, we are probably including many blastomatoid growths.

Fig 133 Tibia and fibula showing multiple exostoses

Osteomata grow from the periosteal or the medullary surfaces of bones as indolent, rounded, or lobulated tumours composed of compact or cancellous bone; they are often multiple.

The compact ivory osteomata are chiefly found in connection with the *bones of the skull. They are not* uncommon in the external auditory meatus or the nose, and may give rise to complete obstruction of the passages concerned; while if they happen to arise in the orbit, they may displace and destroy the eyeball.

The osteochondromata occur at the ends of long bones in young adults They are nodular cartilaginous tumours having an osseous pedicle protruding through a periosteal gap in the bone and commonly arise at the point of attachment of a tendon. Microscopically they are found to have a covering of connective tissue merging with the tendons; under this is a zone of cartilage with

[1] Geschickter, C. F. and Copeland, M. M., *Tumours of Bone*, New York, 1936, is a useful monograph to consult.

calcification in its deepest layers and blending with normal laminated bone of the pedicle which is continuous with the corticalis of the bone from which the tumour arises. It is considered that these growths represent a failure of accurate approximation of the tissue forming the junction between a tendon and its cartilaginous insertion with the result that the connective tissue in the tendon undergoes a

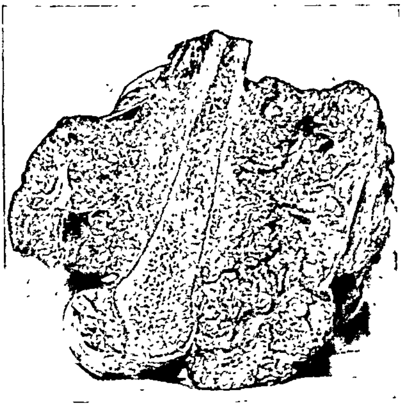

FIG. 134 Massive chondroma of the lower end of the femur

proliferative cartilaginous metaplasia and there is an exaggeration of the normal bony protruberance at such a point.

The **enchondromata** occur centrally in small bones, sternum or ribs of adults between the ages of twenty and thirty; they are rarely multiple They cause an enlargement of the bone with a thinning of the corticalis and consist of a mixture of cartilage cells and primitive connective tissue which may be myxomatous; they may undergo ossification Unless completely removed they are liable to recur and those arising in the ribs and sternum rarely undergo malignant change.

There is a familial condition—diaphysial aclasis or hereditary deforming chondrodysplasia in which multiple exostoses are associated with gross bony deformities and central chondromata; it is interpreted as a congenital disturbance of the perichondrium.

Chondromata also arise in the respiratory tract, from cartilage in glottis, trachea and bronchi.

Fibromata may grow from the periosteum or in the medullary cavity. They may form firm hard tumours which often show a certain amount of ossification ; or they may be vascular and highly cellular, when it becomes difficult to separate them from the fibrosarcomata. The softer tumours are liable to exhibit myxomatous degeneration.

Myxomata, lipomata, and **angeiomata** are rare tumours which may occur in the substance or on the surface of bones.

Osteoclastomata (giant-celled tumours) cannot be classed among the innocent tumours of bones. They give rise to a considerable destruction of the normal tissues and some have produced metastases (p. 88).

Myelomata have been referred to elsewhere. Inasmuch as they are derived from the marrow they do not really belong to the tumours of bone, but they may be mentioned here for the sake of convenience.

Malignant Tumours. The primary malignant tumours of bone are all of the connective-tissue group ; carcinomata are invariably secondary.

Osteogenic Sarcoma. Osteogenic should mean a tumour arising in bone. It is sometimes used for a tumour in which bone develops. It is properly used for all tumours arising in bone, but not for those arising in bone marrow, blood vessels or other tissues in or near bone unless they are capable of forming bone. Bone is a special connective tissue which may develop in fibrous or cartilaginous tissue and it will follow that its tumours may contain osseous, fibrous or cartilaginous tissues or mixtures of these. Throughout life bone is constantly being eroded and new bone made so that it is even in old age well practised in cell proliferation.

The osteogenic sarcomata are divided into the sclerosing and osteolytic varieties. Both forms occur in young adults and arise most frequently about the knee joint. In the sclerosing type the tumour arises in the subperiosteal tissue and spreads outwards forming the characteristic radiating spindles of bone and involves the medullary cavity secondarily, whereas the osteolytic variety arises in the medullary cavity with destruction of medulla and cortex and considerable tendency to pathological fractures. The tumours of the sclerosing type are firm and whitish with a variable degree of osteoid tissue and histologically range from a tumour consisting to a large extent of closely set abnormal trabeculæ to a polymorphic cellular tumour with little bone formation. The osteolytic tumours are extremely vascular corresponding to the telangiectatic variety or

malignant aneurysm of bone of older writers and have a polymorphic histology. The sclerosing variety have a 25 per cent. five-year cure, whereas the osteolytic have only a 10 per cent. five-year cure.

In classifying osteogenic sarcomata either their histological structure or their origin in bone could be used as a basis. The histological classification would be osteosarcoma, fibrosarcoma, chondrosarcoma and mixed osteo-fibro-chondrosarcoma. This is not so useful in practice as a classification based partly on histology and largely on situation. The classification suggested by Ewing for the Bone Registry of America is:

1. (a) Medullary.	4. Periosteal.
(b) Subperiosteal.	5. Fibrosarcoma. (a) Medullary.
2. Telangiectatic.	(b) Periosteal.
3. Sclerosing.	6. Parosteal.

Medullary and Subperiosteal Osteogenic Sarcoma. These tumours may be mostly within the corticalis of the bone or mostly confined by the periosteum. Eventually, of course, they will infiltrate and extend beyond these structures. They are composed of round, spindle and polygonal hyperchromatic cells which produce fibrous, ostoid, osseous and cartilaginous tissues in varying amount and all mixed in a complex and haphazard pattern.

Telangiectatic Osteogenic Sarcoma are very hæmorrhagic tumours in which the tumour cells and tissues form an outer shell surrounding the central part consisting largely of blood and necrotic tissue.

Sclerosing Osteogenic Sarcoma. In these tumours the osseous tissue so predominates that a hard ivory-like mass results.

Periosteal Osteogenic Sarcomata form spindle-shaped masses around the bone with the minimum erosion of the corticalis. The tumours vary in their histological picture, small spindle cells, more mature fibrous tissue, dense fibrous tissue and osteoid tissue may be found.

Fibrosarcomata—medullary or periosteal—are tumours consisting almost entirely of dense fibrous tissue. These are slow growing and relatively avascular. The cells are mostly spindle cells and the fibre and matrix predominate; some osteoid tissue and calcification or ossification may be found.

Parosteal and Capsular Osteogenic Sarcoma. Osteogenic tumours may involve any of the joints and others may arise in the neighbourhood of bones though not directly from them.

It will be realised that a classification of this kind may explain the type of shadow produced on X-ray examination and may be of clinical

use but has little pathological meaning. All these tumours are highly malignant, but those which are most cellular and least differentiated are the most malignant.

Chondrosarcomata (or chondromyxosarcomata) may be sharply divided into a primary and secondary group. The primary chondrosarcoma arises in the periosteum and does not at first involve either the cortex or the medulla of the bone. They occur in young adults most frequently at the knee or shoulder joint at a point of tendonous attachment and form firm cartilage-like tumours breaking through the periosteum to spread into the surrounding tissues and at a later stage the medulla of the bone. Histologically they are formed of pleomorphic cartilage cells with little tendency to ossification. They metastasise early and have a very poor prognosis (12 per cent. of five-year cures).

The secondary chondrosarcomata arise either in relation to an exostosis or more frequently an enchrondoma. They occur about the fourth decade and are found most frequently in the upper end of the humerus and lower end of the femur. The medullary type cause a central osteolysis with a slight periosteal reaction and form a compact translucent tumour microscopically consisting of poorly differentiated chondroblasts in a myxomatous stroma. Metastases are late and there is a 25 per cent. of five-year cures.

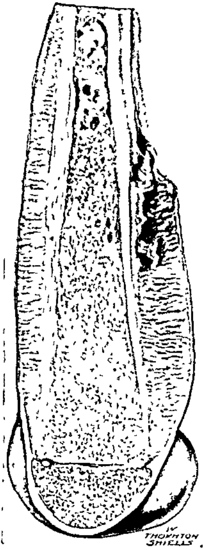

FIG. 135 Sub periosteal osteogenic sarcoma of the femur which has invaded the medullary cavity. There is much bone formation, and bone spicules can be seen radiating out from the shaft (cp Fig 136)

In addition to osteogenic sarcomata other tumours arise in bone, but are not essentially bone tumours. They are angeiomata, tumours of blood-forming tissues, reticulo-sarcoma, lipo-sarcoma, Ewing's

endothelioma of bone and adamantinoma of tibia. **Ewing's tumour**[1] *occurs most frequently in young subjects,* generally before the twentieth year. It affects flat bones and the shafts of long bones. It may be single or multiple. Though highly malignant it is very radio-sensitive. *The patients often have a temperature and a history* suggesting a subacute osteomyelitis. The tumour may be localised, but

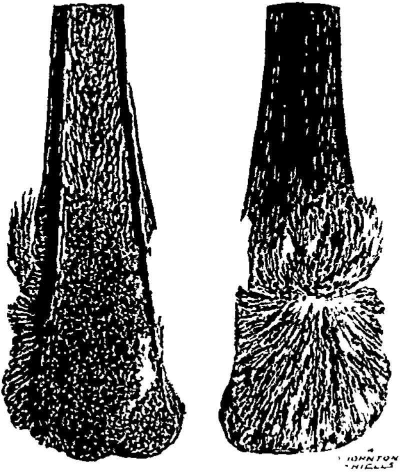

FIG. 136. Macerated specimen of a sclerosing osteogenic sarcoma of the lower end of the femur, showing the formation of bone.

more often it spreads through the shaft producing a rarefaction and swelling of the bone. The tumour is made up of solid masses of polygonal or round cells without inter-cellular material. Their nuclei are small hyperchromatic and nucleoli are not usually seen. There may be slight grouping of the cells, but usually in a section they appear as sheets. The origin of the cells of the tumour is in doubt. Ewing and others believe that they are derived from angeioblastic endothelium,

[1] Stout, A P , *Am. Jl. Roentgenol* , 1943, 50, 334

others believe that they are derived from reticulo-endothelium. There is no good reason for doubting that tumours may arise from endothelium in bone. Ewing's tumour does not, however, appear to arise from endothelium elsewhere. Although the origin of the cells is in doubt there is none about the existence of the tumour, but it may be closely mimicked by secondary tumours from primaries in kidney or adrenal.

Tumours closely resembling **adamantinomata** sometimes arise in the tibia. It is difficult to believe that they arise from ectopic enamel organ and their origin is unknown.

Secondary Tumours. In certain forms of carcinomata metastases are very commonly found in the bones, chiefly the vertebræ, the ribs and sternum, the femur, the humerus, and the bones of the skull. This is especially frequent in carcinomata of the breast, prostate, thyroid, bronchus and suprarenal neuroblastomata. Another form of tumour which may give rise to bony deposits is the malignant hypernephroma.

Invasion of the bone may be the result of vascular embolism, lymphatic permeation, or the direct extension of the primary growth or its metastases. The metastases may be situated on the surface or in the cavity of the bone.

Secondary carcinoma may cause absorption of bone (osteoclastic or osteolytic) or excite abnormal deposition (osteoplastic or osteosclerotic). Spontaneous fractures are commonly associated with the abnormal absorption. The abnormal deposition may be so great that the blood-forming tissue is detroyed and leuco-erythroblastic anæmia result. There is a peculiar tendency of carcinomata of prostate to excite abnormal deposition of bone and for most of the very cellular or hæmorrhagic growths such as chorion carcinoma or Grawitz's carcinoma (hypernephroma) to produce destruction of bone.

Secondary sarcomata of bone are much less common, but the round-celled tumours are liable to form deposits in the skull bones, and the skeleton may be extensively invaded in generalised melanotic sarcoma.

THE CIRCULATORY SYSTEM

THE HEART AND PERICARDIUM

Primary cardiac tumours are extremely rare. Among the benign neoplasms, **fibromata, lipomata** and **angeiomata** are described as growing from the pericardium and in the wall of the heart itself; in the latter situation the tumours usually form polypoid masses covered

by endocardium. The commonest tumour is a fibromyxoma which arises most commonly from the region of the annulus ovalis and most often projects into the left auricle although it may project into the right. Some of these are true blastomas and may be the origin of sarcomas; others may be local hyperplasias or organised thrombi. When they reach the size of an egg or larger, and particularly if pedunculated they may block either the mitral, or, if arising from the right side, the tricuspid orifice. Two interesting tumours, probably *congenital in origin, that have been recorded as occurring in the* myocardium are the **rhabdomyoma** and the **myxoma.**

Primary malignant tumours are also very uncommon. An **endothelioma** is said to occur in the pericardium, and **sarcomata** may be met with in the heart wall.

Secondary tumours are more often seen. The pericardium may be directly invaded by intrathoracic and mammary tumours, and both it and the heart may present metastatic growths, though, as a rule, only in advanced cases of malignant disease. The commonest secondary tumour is from carcinoma of bronchus. This is often a direct spread around the pulmonary veins and may produce a mass in pericardium, myocardium or projecting within an auricle.

THE BLOOD AND LYMPH VESSELS

Primary blastomata are practically unknown in the larger vessels, though a **myomatosis** may be encountered in connection with the walls of the smaller arteries and veins.

From the capillaries originate the various forms of **angeiomata** (p. 186), and the **endotheliomata** are derived from the lining cells of both blood and lymph capillaries. Under the name ***perithelioma*** *some* authors include a special class of endothelioma derived from perivascular lymphatics, but the term is more commonly used as a description of tumours having a striking perivascular orientation.

Secondary Growths. The rôle of the vascular and lymphatic channels in the dissemination of malignant growths has already been fully discussed (p. 28 *et seq*).

THE LYMPHATIC GLANDS

The neoplasms of lymphadenoid tissue have been considered in Part II (p 92). A true benign blastoma of lymphatic glands is rare, but primary malignant tumours are not infrequent, and the various forms of reticulosarcomata and their mode of spread have already been described (p 108).

Secondary growths occur earlier and with greater frequency in the lymph glands than in any other organ of the body, and it is no exaggeration to say that an accurate knowledge of the lymphatic system is the key to the successful surgical treatment of malignant disease The carcinomata, of course, almost invariably form metastases in lymph glands; sarcomata, contrary to the generally accepted teaching, very frequently do the same, though in these tumours dissemination by venous channels is often of greater importance.

Often lymph nodes in the drainage region of a neoplasm show a marked proliferation of the sinus lining cells producing the appearance known as sinus catarrh. This should be carefully distinguished from metastatic infiltration and is not a pre-malignant change, but may be found in any lymph nodes draining areas of cellular necrosis.

THE SPLEEN

Primary tumours of the spleen are comparatively rare. The commonest are angeiomata which are usually benign hæmangeiomata, but are sometimes malignant The benign angeiomata are sometimes more clearly seen naked eye because they may so mimic the structure

FIG 137 Vascular dissemination in the spleen, secondary to carcinoma of the breast Masses of carcinoma cells lying in the spleen pulp, and in a large vein; a large column of cells can be seen passing into the vein.

Zeiss Obj. aa Comp. oc. 6. Tube length, 160 mm.

of the spleen that they are difficult to indentify histologically. Fibromata are also found. Reticulo-sarcomata of all types arise in the spleen.

Secondary Tumours. It is curious to note the relative immunity of the spleen to secondary growths. The organ may be invaded by direct extension from an adjacent organ, or by secondary deposits in the glands in the hilum, but true metastatic tumours are uncommon, but by no means as rare as is generally supposed. Kettle [1] described an interesting form of diffuse malignant infiltration of the spleen, unaccompanied by any macroscopic evidence of the condition, as occurring in cases of carcinoma of the breast (Fig. 137, and p. 138).

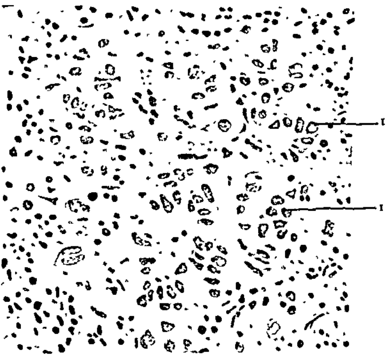

FIG. 138. Microscopic section of a spleen showing diffuse malignant infiltration secondary to carcinoma of the breast (1) Carcinoma cells.
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THE RESPIRATORY SYSTEM

THE NASAL CAVITY AND ACCESSORY SINUSES [2]

Innocent Tumours. Quite the commonest tumour is the **nasal polyp,** but only occasionally can this be regarded as a true neoplasm. In the majority of cases it represents merely a localised hypertrophy

[1] Kettle, E. H. *Journ Path and Bact*, 1912, **17**, 40

[2] Ringertz, N. *Pathology of Malignant Tumours arising in the Nasal and Paranasal Cavities and Maxilla*, Helsingfors, 1938, is an excellent monograph on the tumours of this region

of the mucous membrane, and is composed of loose, oedematous connective tissue, covered with a layer of epithelium and often containing a few gland tubules. Sometimes the polypi appear to be of inflammatory origin, consisting of oedematous fibrous tissue, fairly rich in cells, and containing many delicate capillary vessels, around which are small collections of mononuclear leucocytes. However, true polypoid **adenomata** and **fibromata** do occur, though not often. Fibromata of the septum sometimes arise in young adults (particularly males) and show a considerable liability to bleed and local recurrence.

Other innocent tumours are angeiomata, osteomata [1] and chondromata. Ganglioneuromata occasionally arise in the upper part of the nasal cavity in infants. Other uncommon tumours are chordomata and plasmomata.

Malignant Tumours. Sarcomata may occur primarily in the nose or in the accessory sinuses. Fibrosarcomata and reticulosarcomata are the usual forms, and a chondrosarcoma may occasionally be seen.

Carcinomata are uncommon. They may be either of an atypical squamous-celled, or an adenocarcinomatous type. Ewing has described an undifferentiated polyhedral cell carcinoma believed to be derived from Schneiderian epithelium, and lympho-epitheliomata will be dealt with in the section on the tonsil (p 233).

THE LARYNX

Innocent Tumours. Innocent tumours of the larynx are of unusual importance, for, from their situation, they may give rise to serious respiratory embarrassment as well as aphonia. Simple **papillomata** are the commonest tumours, the next in order of frequency being the **fibromata. Lipomata, myxomata, angeiomata, chondromata,** and **adenomata** have all been recorded as occurring in the larynx, but have very little practical importance.

Papillomata occur as localised or diffuse warty growths, usually springing from the vocal cords (Fig. 139). They are composed of connective-tissue processes covered with an hypertrophied squamous epithelium, and many of them are undoubtedly of inflammatory origin. They tend to recur after removal, but seldom assume true malignant characters. **Fibromata** may be sessile or pedunculated, and they also arise as a rule from the cords.

[1] A special monograph on the bony tumours of the nose and sinuses has been written by Prof C. E. Benjamin (Edition Delmas, Bordeaux, 1939).

Malignant Tumours. Sarcomata are rare. They are usually of the round- or spindle-celled variety, though fibro- and chondrosarcomata also occur.

Carcinomata are by no means infrequently seen, growing from the cords or the mucous membrane below them, the epiglottis, or the

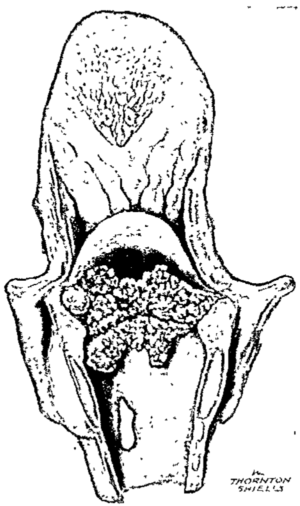

FIG 139. Larynx and trachea opened from behind to show multiple papillomata.

pyriform fossæ. They usually form papillomatous or warty tumours, and are almost invariably of the squamous-celled type, though adenocarcinomata, and a scirrhous carcinoma simplex have also been recorded.

As a rule, laryngeal carcinomata remain fairly well localised to the throat and the cervical glands, but occasionally they may form distant metastases There is a considerable difference in the prognosis and response to radiotherapy of hypopharyngeal carcinomata according to

their site of origin. The growths most commonly arise in the pyriform fossa and have a poor prognosis.[1]

THE LUNGS AND BRONCHI

Apart from those arising in the bronchi primary tumours of the air passages are rare. In the **trachea** fibromata, chondromata, osteomata, and other connective tissue tumours may be found. Papillomata, adenomata and carcinomata are a little commoner and the carcinomata may be either squamous celled or tubular cubical and columnar celled. The tumours of the **bronchi** are far commoner and with the rise of

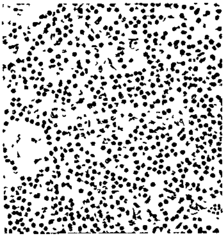

FIG. 140 Small polygonal-celled "adenoma" of bronchus.

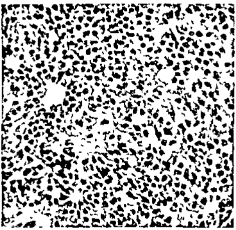

FIG 141 Large polygonal celled "adenoma" of bronchus

thoracic surgery have been much written about and investigated. The benign connective tissue tumours are very varied and most of the connective tissues have been described amongst them; they are all rare, but chondromata, fibromata and myomata are the commonest.

The benign epithelial tumours are **adenomata** and may be either sessile, polypus or papillary They are commoner than the benign connective tissue tumours. They produce signs and symptoms because of bronchiectasis or collapse due to blocking a bronchus or because of hæmoptysis. Although called adenomata most of them infiltrate their stalk or the bronchus in which they arise. The bronchial mucosa may remain intact over them and when it does, it often shows squamous celled metaplasia. Their histological picture varies. It may show solid acini or trabeculæ of small polygonal cells, having well-

[1] For an analysis of results of treatment see Schinz, H. R. and Zuppinger, A., *Arch. f. klin. Chir*, 1936, **187**, 582

formed round or oval nuclei. Sometimes the cells appear in sheets and rarely tubules lined by cubical or columnar cells are found. In any one tumour the cells are usually all of the same kind and vary little in size and shape ; mitotic figures are rare. The amount of connective tissue varies from very little to an abundant wide stroma ; they all have a rich blood supply. The patients usually give a long history, some as long as fifteen and twenty years.

Sarcomata of the bronchi or lung are very rare.

Bronchial carcinoma is by far the commonest and most important tumour. In the standardised cancer mortality rates for men it is the fourth commonest cancer. The development of thoracic surgery, the evidence published by Barnard following a suggestion of Turnbull's that the majority of tumours previously diagnosed as mediastinal sarcomas were in fact bronchiogenic carcinomas, and the fact that some of the tumours are exceptionally frequent among certain mine workers have all contributed to focus attention on these tumours. This has resulted in a widely held belief that there has been a great increase in their incidence. This apparent increase is probably due to three factors : (1) a slight actual increase, (2) improvement in diagnosis, and (3) fashion in diagnosis.

An anatomical classification is the most useful from the points of view both of the clinician and the radiologist.

Type I. Bronchial Tumours. (*a*) In this group the tumours show little tendency to spread beyond the bronchial wall. The mucosa over them is usually intact, although they may project into and even completely occlude the lumen of the bronchus.

(*b*) The tumour spreads along the bronchus, often towards the hilum and peripherally, without infiltrating the lung.

(*c*) Small inconspicuous tumours invading all the walls of a bronchus, often unexpected findings associated with secondary tumours, these latter being *responsible for the patient's symptoms*.

Type II. Peripheral tumours arise in a tertiary or even smaller bronchus, infiltrate the lung and tend to grow peripherally and not towards the mediastinum. Their most characteristic appearance is that of a compact, almost completely round, oval or pyramidal tumour involving the whole or greater part of one lobe surrounded by a shell of collapsed lung, but not involving its hilum. The pleura may be involved and later the tumour may spread by direct extension and invade the chest wall. Metastases are late.

Type III. Hilar tumours arise in the main or early part of secondary bronchi and usually invade the surrounding lung and by direct

infiltration the hilar and mediastinal connective tissues. Often the great veins of the mediastina, the pericardium and less frequently the myocardium are all involved. Secondaries in mediastinal lymphatic glands are the rule and widespread metastases are common.

Unfortunately the **histological appearances** are not peculiar to any of these different anatomical types All the tumours probably arise from the germinal cells in the deepest layers of the multi-layered columnar epithelium of the bronchi. These cells can differentiate in two ways :

```
                         Germinal cells
                               |
        ---------------------------------------------------
        |                                                 |
    Polygonal                                          Cubical
        |                                                 |
    Transitional                                       Columnar
        |                                                 |
    Squamous                                           Mucous
        |
    Squamous prickle
       and horny
```

The germinal cells themselves are oval and a tumour may be composed mainly of oval anaplastic cells ; or the cells may differentiate and produce any of the other types of cell. Many tumours are composed of mixtures of these cells ; in some one type predominates and in a few the tumour is composed entirely of one type. The histological classification will vary with the investigator, but all who have examined reasonable numbers of tumours agree that the anaplastic and the predominantly anaplastic are commonest, the squamous come next and the columnar celled are the least common.

Anaplastic Carcinomata. These consist for the most part of "oat" cells arranged in a diffuse, trabecular or solid acinar manner. The cells are in the main oval and, when cut transversely, round and have little cytoplasm. The nuclei are oval and in some cells have a distinct chromatin net with chromatin nodes and in others the whole nucleus is so deeply stained that its structure is obscured. In many of the tumours polygonal and giant cells may be found and in some the cells may be grouped as if to form tubules

Squamous celled, as their name implies, are composed of polygonal cells arranged as a pavement of closely opposed cells, some of which may have "prickle" borders and some become keratinised to form "horny pearls." Other tumours may be largely composed of transitional epithelium.

Tubular, Alveolar, Cubical and Columnar Celled. This group includes all the tumours in which well-formed tubules and alveoli are found. Papillæ often project into the alveoli and some of the tumours are

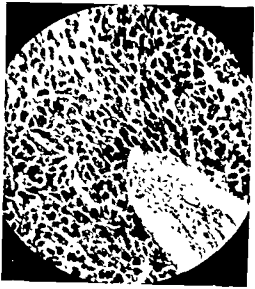

FIG 142. Anaplastic carcinoma composed mostly of "oat" cells.

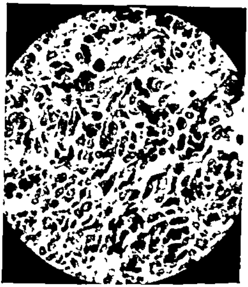

FIG. 143. Anaplastic carcinoma of mixed cells, some "oat," some polygonal.

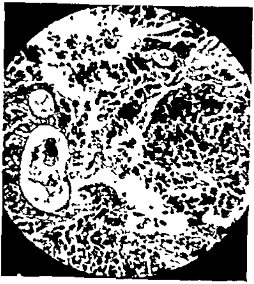

FIG. 144. Partly anaplastic and partly tubular cubical-celled carcinoma.

FIG 145 Squamous and prickle-celled carcinoma of bronchus.

mucus secreting. In one type of this tumour the tall columnar cells infiltrate the lung alveoli giving an appearance of alveoli lined by tall columnar sometimes ciliated mucus secreting epithelium, but thorough search always reveals the source of the growth in a bronchus.

There is no good evidence for carcinoma arising in alveoli, although as a very rare tumour it may arise in alveoli which have become lined by a downgrowth of epithelium from a bronchiole.

Endothelioma of the pleura is a rare tumour and in many cases which have been so diagnosed it is probable that the tumour was in fact secondary to an inconspicuous bronchial primary growth.

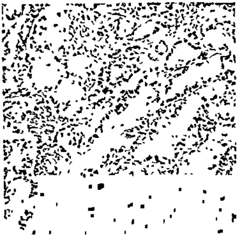

FIG 146 Tubular columnar-celled mucous carcinoma of bronchus

FIG. 147. A higher power picture of a part of Fig. 146.

Secondary Tumours. Pulmonary metastases are of frequent occurrence in all forms of malignant disease, most of them developing from vascular emboli. Permeation of subpleural and peribronchial lymphatics also occurs particularly in carcinoma.

Sometimes secondary peribronchial carcinomatous infiltration is general throughout the lung. When this occurs the radiological picture and the naked eye appearance of the lung is very like that found in generally disseminated tuberculosis.

THE ALIMENTARY SYSTEM

THE LIPS

Apart from **papilloma, innocent tumours** of the lips are rarely of any importance, but angeiomata are not uncommon in childhood.

The **vascular nævus, or capillary angeioma,** may grow on the mucous or the cutaneous surface : it is a congenital tumour, though it may

be quite small at birth. The condition of congenital hypertrophy of the lip, known as **macrocheilia**, is due to a **cavernous lymphangeioma.**

Retention cysts of the mucous glands are not uncommon, and occasionally neoplasms resembling the " mixed salivary gland tumours" are found *probably arising from salivary glands in the submucosa of* the lip

Malignant Tumours. The **squamous-celled carcinoma** is a fairly common tumour in men over forty years of age ; it is rare in women. It is usually associated with some form of chronic irritation, and is especially liable to appear in smokers who are in the habit of using a clay pipe. In untreated cases the growth extends locally to the jaw, and instances are recorded of infection of the other lip from direct contact ; metastases also form in the submaxillary and submental lymph glands, but there is seldom any widespread dissemination.

THE TONGUE

Innocent Tumours. The innocent connective-tissue tumours are not often seen, but **fibromata, lipomata, angeiomata** and **myxomata** may occur, usually early in life. A curious tumour is a rhabdomyoma or rhabdomyosarcoma in which the cells are short and fat with granular protoplasm. **Macroglossia,** or congenital hypertrophy of the tongue, may be caused by a **cavernous lymphangeioma.**

Black hairy tongue is a hyperplasia of the filiform papillæ associated with fungal infection.

The innocent **squamous papilloma** is less common than the malignant *epithelial growths, and is always to be regarded with suspicion.*

Dermoid cysts are sometimes encountered in the mid line of the floor of the mouth.

A rare tumour is one derived from remnants of the **thyroglossal duct.** It is situated in the base of the tongue, and is usually cystic.

Malignant Tumours. Sarcomata are not very common. They may be fibro-, myo- or of the round-celled and lymphosarcoma type, and a very careful microscopic examination may be necessary to distinguish them from conditions of chronic inflammation

The **squamous-celled carcinoma** is the commonest of all the tumours of the tongue It most often occurs in men between forty and sixty years of age, and may be of the ulcerative, papillomatous, or nodular type. The growth very frequently follows on prolonged irritation from a jagged tooth or a pipe stem, or it may be preceded by a chronic superficial glossitis or a syphilitic leucoplakia. The prognosis, no

matter which type of treatment is adopted, is directly related to the situation, growths nearest the tip giving the best and those furthest back the worst prognosis. Lymphatic dissemination takes place early in the disease, the glands on both sides of the neck being involved.

It is comparatively rare for metastases to form in other parts of the body, and in forty-three consecutive autopsies on cases of advanced carcinoma of the tongue and mouth secondary growths were found only four times in the lungs, twice in the liver, and once in the stomach, axillary, and tracheobronchial glands. There is, however, widespread local extension with ulceration, and the cervical metastases tend to break down and fungate, so that the last stage of the patient is pitiful in the extreme. Death usually results from septic absorption, bronchopneumonia, or hæmorrhage from the cervical vessels A point to be emphasised, one having an important bearing on the prognosis, is the difficulty there may be in demonstrating the cervical metastases in early cases. Kettle more than once made an extremely careful examination of the contents of the cervical triangles removed at the same time as the tongue, without success ; nevertheless, the patients returned within a few months with large masses of growth in the neck.

THE MOUTH, PHARYNX, AND TONSILS

Benign tumours of the oropharynx are uncommon, though **fibropapillomata** are sometimes found on the tonsils and a **mixed salivary gland tumour** may arise in the small glands of the hard palate. **Reticulosarcomata** of the tonsil are not infrequent and are usually of the lymphoid type. They are extremely radiosensitive and in cases which are not systematised have a comparatively good prognosis.

Carcinomata of the tonsils and fauces are of two types—the squamous cell carcinoma, which have no remarkable features, and the lymphoepithelioma

Ahlbom [1] has suggested that pharyngeal carcinoma in women only arises in those suffering from chronic hypochromic anæmia with atrophy of the mucous membrane.

Lymphoepitheliomata [2] (Schmincke tumours ; transitional cell carcinoma of Ewing) may arise anywhere in the nasopharyngeal area and more rarely in the thymus and particularly in the ring of Waldeyer. These tumours are epitheliomata arising in lympho-epithelium and show the merging of the epithelial and lymphoid cells so characteristic

[1] *B.M J*, 1936, **2**, 331
[2] D F. Cappell, *J. Path. and Bact*, 1934, **39**, 49.

of this tissue, but it is only the epithelium which has undergone a neoplastic change and though the metastases may show a lymphotropism there is no suggestion of a mixed neoplasm.

The primary tumour is commonly quite small and may only be detected after careful searching and it is usual for the presenting symptom to be enlargement of cervical lymph nodes and neuralgic pain or deafness as a result of pressure on the nerves. There is considerable tendency for infiltration into the skull with involvement of the orbit or meninges.

Microscopically the tumours consist of sheets of poorly differentiated epithelial cells often in synplasmic form lying in a lymphoid stroma. The demarcation between the epithelial and lymphoid elements may be difficult to make out. Lymphoepitheliomata have been mistaken for reticulosarcomata and *vice versâ*. In reality the nucleus of a reticulum cell with its fine strands of chromatin in no way resembles the vesicular nucleus of an epithelial cell and the pattern of the reticulin network in the two tumours is quite different.

Lymphoepitheliomata are extremely radiosensitive, but as symptoms do not commonly develop until there has been considerable spread of the growth the prognosis is poor.

THE JAWS

The innocent connective-tissue tumours are the **fibromata, myxomata, osteomata,** and **chondromata** ; they are not common.

The **myeloid epulis**[1] (osteoclastoma), growing from the alveolar margin, has a certain degree of local malignancy. It is composed of a cellular connective-tissue stroma in which appear numerous giant cells of the osteoclast type (*Fig. 148*). *It is to be distinguished from various* chronic inflammatory formations.

Different types of solid and cystic tumours may grow in connection with the teeth, and much confused terminology has resulted, but for all ordinary purposes it is sufficient to recognise three types—odontomes, paradental epithelial cysts and adamantinomata

The **odontomes** are mixed tumours composed of a mass of poorly formed teeth or a complex of enamel, cement, and dentine and are surrounded by a fibrous capsule ; they grow slowly, gradually expanding the jaw and are found in children or young adults usually at a point where there is an unerupted tooth.

[1] Noeppel has written a useful monograph on the epulides, *Morphologie des Épulis*, Paris, Masson et Cie, 1938.

The **paradental epithelial cysts** occur most frequently in the upper jaw in the third decade, they may cause thinning of the bone and are occasionally multilocular; they are lined by stratified epithelium, but if there has been secondary infection may only show a granulation tissue membrane. Unless they are completely removed there is a considerable liability to recurrence.

The **adamantinomata** have already been described (p. 87) and

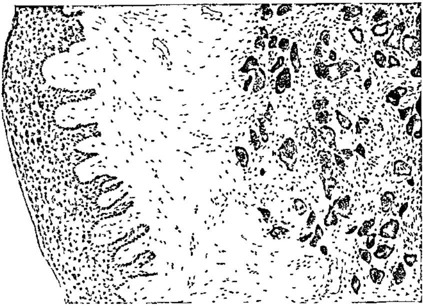

FIG 148 Microscopic section of a myeloid epulis of the jaw (1) Surface epithelium, (2) sub-epithelial connective tissue, (3) tumour tissue consisting of giant cells embedded in a cellular stroma.

Obj 16 mm apochrom. Comp oc. 4. Tube length, 160 mm

form solid tumours with a firm elastic consistency and although essentially benign are liable to recur locally

Malignant Tumours. Sarcomata are rather more common in the upper jaw than the lower. They may be of the round- or spindle-celled type, or the more slowly-growing fibro-, osteo-, or chondro-sarcomata.

The **squamous-celled carcinoma** grows from the alveolar surface, and a somewhat atypical example of this tumour occurs in the antrum of Highmore.

THE SALIVARY GLANDS

Salivary gland tissue may be found anywhere in the mouth, tongue, cheek or palate as well as in the parotid and submaxillary glands;

and because of this, salivary gland tumours may arise in any of these situations.

Innocent Tumours. **Fibromata, myxomata, chondromata, rhabdomyomata,** and **angeiomata** have been described, but it is probable that the majority of them are really instances of the predominant growth in a mixed salivary gland tumour.

A cyst of the duct of a salivary gland may be found anywhere in the

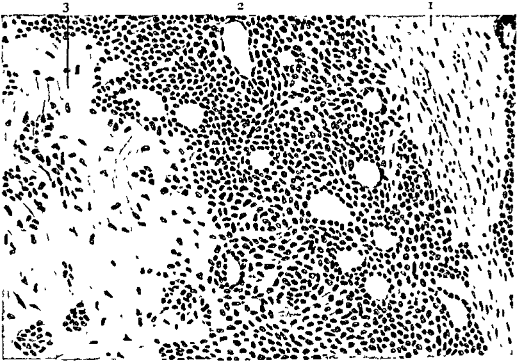

FIG 149 Microscopic section of mixed tumour of the submaxillary gland (1) Connective tissue stroma; (2) dense mass of tumour cells showing the formation of irregular spaces, (3) area in which the growth has undergone myxomatous degeneration.

Obj 8 mm apochrom. Comp. oc 6. Tube length, 160 mm.

floor of the mouth and when it forms a purple blue swelling it is called a ranula.

The simple **adenoma** is rare.

Malignant Tumours. **Sarcomata** are very uncommon and are, as a rule, highly malignant.

Carcinomata. Adenocarcinomata and squamous-celled carcinomata do occur, though not often.

By far the commonest tumour of the salivary glands is the so-called "**mixed parotid tumour,**" which, though it occurs chiefly in the parotid gland, also grows in the submaxillary gland palate and occasionally in other situations This tumour has given rise to a great deal of discussion, and it was formerly the fashion to call it an endo-

thelioma; but it is now pretty well agreed that it is derived from epithelium, probably from the cells of the duct of the gland.[1]

The parotid tumour forms a slowly growing, lobulated mass, which usually shows only a slight degree of malignancy. It may have been present for years, and have reached an enormous size, without showing any infiltrative growth and without forming metastases. Nevertheless, it frequently recurs after removal, since isolated lobules may escape notice at the operation.

On section it is fairly firm, and has a semi-translucent surface,

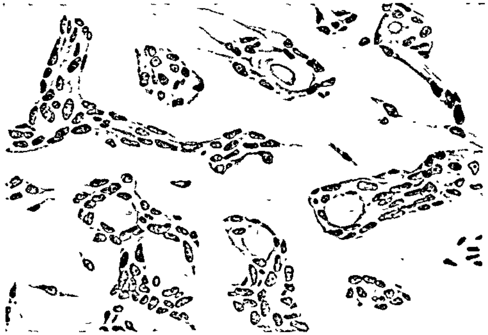

FIG. 150. Microscopic section of mixed tumour of the parotid gland. The tumour is composed of myxomatous tissue in which lie groups of epithelial cells which often enclose distinct lumina.

Obj. 8 mm. apochrom. Comp. oc. 12. Tube length, 160 mm.

mottled with whitish areas of denser growth. Some tumours may be soft and gelatinous. *Microscopically* (Figs. 149 and 150) it is composed of groups of cells of a somewhat irregular form; some may be cubical, others are polygonal or flattened. These cells may occur in solid masses, or they may form narrow branching strands, and they frequently line spaces or lumina. Perfectly typical squamous epithelium with prickle cells and keratinisation is sometimes present. A distinctive feature of the tumour is the fact that it tends to undergo mucoid degeneration. The condensed myxomatous stroma encloses isolated tumour cells which become loosened and separated from the main cell

[1] Fry, R. M., *Brit. J. Surg.*, 1927, 15, 291; Sheldon, W. H., *Arch. of Path.*, 1943, 35, 1.

masses so that an appearance closely resemlbing that of cartilage is produced.

The anomalous appearance of the stroma in any salivary gland tumour may well be explained in the way indicated. Tumours having similar histological appearances are sometimes found in the lacrymal gland and in the scalp.

Adeno-lymphoma [1] (Papillary cystadenoma lymphomatosum). These are uncommon tumours arising in salivary glands; they are seldom of large size and are well encapsulated; the cut surface may show a solid white tumour or may be partially cystic with papillary projections. Microscopically they consist of a loculated cyst lined with columnar epithelium lying on a lymphoid stroma showing follicles and Flemming's centres. In some examples the epithelium is more alveolar in arrangement, but there is always a close relationship to the lymphoid tissue. They do not recur if removed completely. There are various explanations as to their origin, but it is clear that they are associated with misplaced embryonic tissue.

Branchial Cysts. Branchial cysts arising as a result of failure of closure of a branchial cleft may occur anywhere in the neck from the tonsillar fossa to anterior border of the sterno mastoid. They may not become apparent until adult life and are smooth-walled cysts containing clear fluid rich in cholesterol crystals. The lining is formed of stratified squamous epithelium on a lymphoid stroma.

Branchial carcinomata are uncommon; they usually arise deep in the neck near the bifurcation of the carotid and form relatively slowly growing but infiltrating growths. They consist of squamous or transitional cells with a considerable tendency to foci of necrosis and the formation of pseudo-cysts.

THE ŒSOPHAGUS

Innocent Tumours. Innocent tumours of the œsophagus are quite uncommon. **Fibromata, myomata, hæmangeiomata, papillomata, lipomata, myxomata,** and **ademomata** are described as occurring in the substance of the wall, or projecting as polypi into the lumen.

Malignant Tumours. Sarcomata are very rare; they are usually of the spindle-celled variety.

Carcinoma. This is the commonest tumour in this region. It is usually of the squamous-celled type, though very occasionally an

[1] Carmicheal, R., Davie, T. B. and Stewart, M. J., *J. Path and Bact*, 1935, 40, 601.

adenocarcinoma may arise from glands in the wall, particularly at the lower end or from misplaced islands of columnar epithelium.

Carcinomata of the œsophagus originate, for the most part, in one of three situations: at the level of the cricoid cartilage, at the level of the bifurcation of the trachea, or at the lower end. Most often the growth is soft and ulcerated, and though it encircles the lumen, no great mass of tissue is formed. Sometimes, however, it is more scirrhous in type, and gives rise to quite a large tumour and may give rise to considerable stenosis. Distant metastases are not often seen, but the neighbouring lymphatic glands are involved Ulceration into the trachea or bronchi, or into one or other of the pleural cavities is common, and a septic broncho-pneumonia or pleurisy is often the terminal event. A patient may die from hæmorrhage as the result of erosion of one of the intercostal branches of the aorta. In œsophageal carcinomata the patients are generally very emaciated from the mechanical interference with nutrition. Although 84 per cent. of all œsophageal carcinomata occur in men, yet 83 per cent. of postcricoid carcinomata are found in women and the average age is significantly lower than that in men ; a study by Ahlbom[1] showed that postcricoid carcinoma in women were usually associated with chronic hypochromic anæmia , this suggests that prevention of this type of anæmia might diminish the risk of this particular type of carcinoma.

A useful statistical analysis of 473 cases of œsophageal carcinoma has been prepared by the British Empire Cancer Campaign.[2]

Dermoid cysts and true **teratomata** are occasionally found in the œsophagus, usually at its junction with the pharynx.

THE STOMACH

Innocent Tumours of the stomach are uncommon, and have comparatively little clinical importance. **Fibromata, myomata,** and the compound **fibromyomata** and **Schwannomata** form small nodular tumours in the substance of the wall ; they may occasionally grow to a considerable size, and sometimes project as polypi into the lumen of the viscus.

Lipomata and **lymphangeiomata** are described as usually occurring under the serous coat. The **adenomatous polyp** is more commonly found ; there is an unusual condition, which may be familial,

[1] Ahlbom, H. E., *B M J* 1936, 2, 331.
[2] *Annual Report of British Empire Cancer Campaign*, 1942, 19, 6

multiple polyposis of the stomach, in which the mucosa shows scattered adenomatous polyps ; there is a considerable liability for malignant change to occur and in a recent review by Spriggs [1] carcinomata had developed in 20 per cent. of the reported cases. Occasionally adenomyoma formed of Brunner's glands or ectopic pancreatic tissue may form solitary nodular masses in the pyloric region.

Malignant Tumours. Sarcomata are rare. Leiomyosarcomata are

FIG 151. Stomach opened to show a massive pyloric carcinoma (A).

the commonest and reticulo-, polymorphic and spindle-cell types also occur.

Carcinoma. Gastric carcinoma occupies a highly important position among the malignant growths, for in England and Wales during 1943, out of a total of 72,151 deaths from cancer the primary tumour was in the stomach in 12,882 cases.

Carcinoma of the stomach is about twice as common in men than in women and usually appears after middle life. In different countries the relative frequency of cancer of the stomach to other sites is very variable ; in England and Wales it forms about 22 per cent of all cases whereas in the United States of America and many European countries

[1] Spriggs, E I, *Quart J Med.*, 1943, 12, 1.

it is between 50 and 60 per cent.; on the other hand, in eastern countries it only forms 2 to 5 per cent of all cancer deaths. In the 1931 Decennial Supplement, the Registrar-General showed that in England and Wales the incidence of gastric carcinoma is significantly

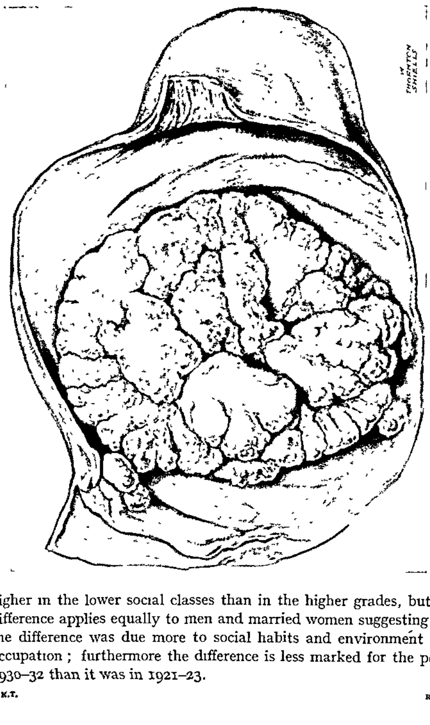

FIG 152 Stomach laid open to show a fungating "cauliflower" carcinoma

higher in the lower social classes than in the higher grades, but this difference applies equally to men and married women suggesting that the difference was due more to social habits and environment than occupation; furthermore the difference is less marked for the period 1930–32 than it was in 1921–23.

There has been considerable discussion as to the part gastritis plays in the liability to carcinoma and as yet no clear evidence is available.

The majority of the carcinomata of the stomach involve the pyloric region or lesser curve, but they may be found in any part.

Of the macroscopic classifications, that of Borrman is the most useful as it bears a direct relationship to the radiological appearances and surgical accessibility. He recognises four main types: (1) A

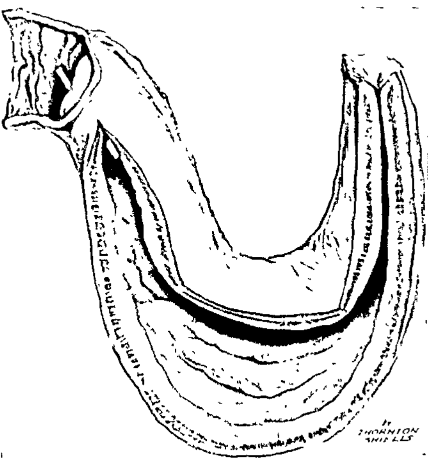

FIG. 153 Scirrhous carcinoma of the stomach ("leather-bottle stomach"); a rod is passed through the pylorus

circumscribed polypous lesion in which ulceration is slight or absent (Fig. 152); this form is uncommon (6 to 8 per cent), but is the most suitable for resection and so has a relatively better prognosis. (2) Sharply circumscribed ulcerated tumours; these are also uncommon and usually occur in the fundus and corpus, but they are fairly amenable to surgery. (3) Ulcerated lesions circumscribed in part of the circumference with ill-defined borders in other parts; this is the commonest type and is mainly localised at the pylorus or less frequently the cardia

(Fig. 151). (4) Diffuse growth throughout the stomach wall without ulceration. In these cases the wall of the stomach is dense and rigid and the lumen is contracted, the condition being known as the "leather-bottle stomach" or linitis plastica (Fig. 153). In another form, the colloid carcinoma, the tumour exhibits mucus secretion. As a rule this form of cancer tends to crop out on the serous surface and spread widely throughout the peritoneal cavity.

Sometimes a very malignant growth may progress so rapidly through the coats of the stomach wall as to give rise to perforation. Histologically the tumours present all degrees between the well-differentiated adenocarcinoma and a spheroidal cell carcinoma; histological criteria are of little value in prognosis. As would be expected the well-differentiated adenocarcinomata have the best prognosis and those with marked mucous change are more malignant than the average; the diffuse scirrhus type, though slow-growing, shows a considerable liability to metastasise and is usually not diagnosed until too late for operation. The cells are mostly polygonal or spheroidal and are often isolated by a fibrous stroma; rarely they are mucus secreting.

Formerly there was considerable debate as to what proportion of simple peptic ulcers underwent malignant change; however, the critical studies of large series of cases by M. J. Stewart[1] and W.D. Newcomb[2] show that about 5 per cent. of all chronic peptic ulcers show malignant change and about 13 per cent. of gastric cancers arise in a pre-existing simple ulcer.

Microscopic examination is essential to determine whether or not a peptic ulcer has undergone malignant change; the fibrous floor and vascular changes together with the fusion of the muscularis mucosæ and muscularis are reliable criteria in distinguishing a carcinoma arising in a chronic peptic ulcer from an ulcerated carcinoma, but regenerative hyperplasia in the mucosa and the presence of misplaced islets of epithelium on the deep side of the muscularis mucosæ render difficult the early recognition of malignant change in a chronic ulcer.

In cancer of the stomach extension is by local spread, and by the lymphatic and vascular channels. The lymphatic glands chiefly involved are those in the lesser curvature and the pyloric portion of the greater curvature, and the group at the cardiac orifice. Frequently the left supraclavicular lymphatic glands are also affected. There may often be metastases in the liver and the lymphatic glands in the portal fissure. Extension of the growth to the outer surface of the

[1] Stewart, M. J., *Lancet*, 1931, 2, 565, 617, 669.
[2] Newcomb, W. D., *Brit. J. Surg.*, 1932, 20, 279

stomach is followed by direct invasion of the neighbouring viscera, especially the pancreas, and general dissemination throughout the peritoneal cavity. The ovaries may often be involved early in this stage by "droppings" of detached groups of cancer cells; this is particularly liable to occur in association with diffuse scirrhous carcinoma of the "leather bottle" type. In these cases the bilateral ovarian tumours may be the presenting symptom and this is one type of cancer that may give rise to Krukenberg tumour of the ovary (p. 287). It is a curious feature that in this type of growth hepatic metastases are uncommon. Very occasionally groups of cells may become detached from the inner surface of the growth and become transplanted on to the mucous membrane of some part of the small or large intestine. It is particularly noteworthy that direct extension to the duodenum never takes place; the growth always stops short at the pylorus.

Secondary tumours of the stomach are rare. Secondary infiltration of the stomach wall by carcinoma of the pancreas is not uncommon.

THE INTESTINES

Innocent tumours of the intestines are not particularly common. In the connective-tissue group the most usual forms are the **fibromata, lipomata, myomata,** and **angeiomata,** together with the compound

FIG. 154. Intestine opened to show a polypoid fibrolipoma. There is ulceration of the mucous membrane above and below the tumour.

FIG. 155. Microscopic section through the stalk of a papilloma of the rectum showing (1) gland tubules; (2) muscularis mucosæ; (3) connective tissue of the stalk.
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

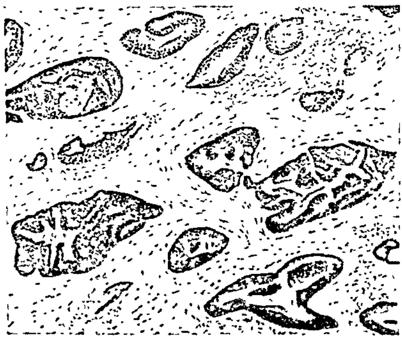

FIG. 156. Section through another part of the stalk of the same rectal papilloma illustrated in Fig. 155, showing early malignant change. The tubules are now extremely irregular, and the structure is that of an adenocarcinoma.
Obj. 16 mm. apochrom. Comp. oc. 4. Tube length, 160 mm.

fibrolipomata and **fibromyomata.** They may be situated in the substance of the wall, or they may project from either surface, being attached by a narrow stalk. The submucous polyp is liable to give rise to ulceration of the adjacent mucous membrane and to a varying amount of mechanical interference with the function of the bowel (Fig. 154). **Adenomata** are somewhat rare except in the large intestine, in the lower part of which sessile or pedunculated papillomata of a moderate size occur. They may be multiple, and there seems no doubt that at times they become malignant (Figs. 155–156). An account of the condition of familial polyposis of the colon is given on p. 123. In the duodenum a papilloma in the region of the papilla of Vater is sometimes encountered, and in the duodenum and jejunum occur small solid adenomata derived from aberrant nodules of pancreatic tissue. In any part of the intestine, but particularly in the

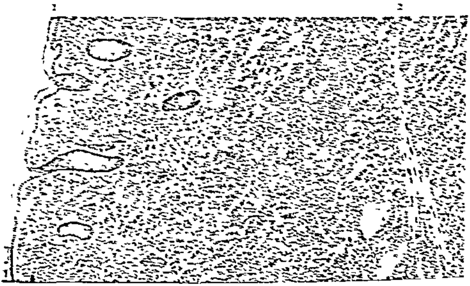

Fig. 157. Lymphosarcoma (reticulosarcoma) of the intestine. The tumour is composed of small round cells lying in a delicate connective tissue reticulum. 1, Epithelium, 2, muscularis mucosae.

Obj. 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

large bowel, polypoid tumours due to some chronic irritative change are not uncommon. They are, of course, blastomatoid in nature, and may be seen in enormous numbers in the healing stage of ulcerative colitis known as colitis polyposa. **Endometriomata** may occur in the serosal and muscular coats of the rectum and less commonly in other portions of the intestinal tract.

Malignant Tumours. Sarcomata. The reticulosarcoma is a not infrequent neoplasm, occurring chiefly in the ileum, the cæcum, and the ascending colon (Fig. 157). Other malignant connective-tissue

tumours are rare, though the round-, spindle-, and polymorphic-celled sarcomata, and the leiomyosarcoma may be encountered. The lower part of the small intestine and the upper part of the large are the sites usually affected; the jejunum is less often attacked, while only about thirty cases of sarcoma of the rectum are on record.

Melanomata are sometimes found in the lower part of the rectum.

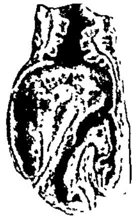

FIG. 158 Lymphosarcoma (reticulosarcoma) of the small intestine forming the apex of an intussusception.

Carcinoma. A considerable proportion, about 10 per cent., of all cancers occur in the intestines, and the great majority of these are large bowel tumours. Carcinoma is a rare growth in the small intestine; Kettle[1] described one of the examples of malignant growth developing in a chronic peptic ulcer. In the neighbourhood of the papilla of Vater a polypoid adenocarcinoma may be met with (Fig. 159), and most of the true carcinomata of the small intestine are adenocarcinomata which may obstruct the lumen.

The commonest carcinoma of the small intestine is the **carcinoid or argentaffin tumours** which probably arise from Kultschitzky cells normally found in the intestinal and appendicular mucosa. They are commonest in the appendix, but also arise in small intestine, stomach and colon. In general they are small yellow masses seen in the mucosa, submucosa, muscularis or subserosa. They may be multiple or single, when multiple they are not usually widely separated. Although they infiltrate and are therefore locally malignant they seldom produce metastases. Their histological structure is characteristic; they consist of solid masses or trabeculæ of cubical or polygonal cells grouped in an orderly arrangement and showing little variation in size, shape or nuclei. When stained by silver many of the cells contain black granules in their cytoplasm.

Carcinoma[2] may occur anywhere in the large bowel, but is commonest in certain situations; more than half the tumours are in the rectum, while other favourite sites are the cæcum and the first part of the ascending colon, the hepatic and splenic flexures, and the sigmoid loop In the rectum the tumour is often oval in shape, and occupies

[1] Kettle, E. H., *Lancet*, 1930, **1**, 570.
[2] Karsner, H. T., and Clark, B., *Am. J. of Cancer*, 1932, **16**, 933

one-third or more of the circumference of the bowel; the surface is ulcerated and depressed, the margins are raised and rolled. Another

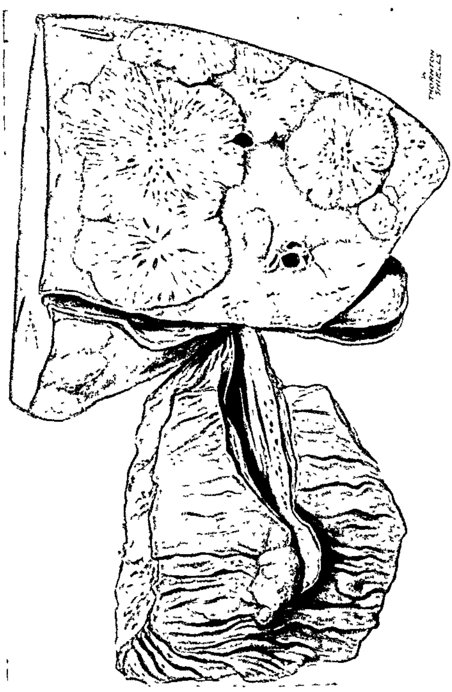

FIG. 159 An adenocarcinoma of the ampulla of Vater showing obstructive dilatation of the common bile-duct and metastases in the liver.

common variety is the annular constricting type (FIG. 161), and this is the form most often seen in the upper part of the bowel. The polypoid tumour is somewhat rarer. Multiple tumours in any organ are very

rare, but are commoner in the large bowel than in any other organ with the possible exception of the breast. Multiple polyps, papillomata, and carcinomata may co-exist (Fig. 162) in the colon or rectum.

The paths of extension of a carcinoma of the rectum are of great importance. Dukes[1] has made a detailed study of this problem and introduced a simple method of classification which is of considerable value in prognosis. In the first instance the growth is limited to

FIG. 160 Microscopic section from the margin of an argentaffin tumour of the small intestine (1) Normal mucous membrane; (2) alveoli of argentaffin cells infiltrating the mucous membrane, and the submucous coat beneath the muscularis mucosæ; acinous formation occurs only occasionally

Obj 16 mm apochrom Comp oc 4 Tube length, 160 mm

mucosa, submucosa and muscularis of rectal wall (type A); there is then a continuity spread through the muscular layers with extension to the extra rectal tissues but no metastases in regional lymph nodes (type B); finally there are lymph node metastases either by emboli or permeation in the regional lymph nodes running in the neighbourhood of the hæmorrhoidal vessels (type C). In a proportion of the cases which have spread into the perirectal fat invasion of the hæmorrhoidal veins may be observed and sometimes there may be secondary deposits in the submucosa distal to the growth due to retrograde venous spread. Invasion of the blood vessels of the mesentery takes place at an early

[1] Dukes, C. E., *J. Path. & Bact.*, 1940, 50, 527.

stage, and emboli are carried to the liver by way of the portal system. In carcinomata of the lower part of the rectum the vascular metastases are sometimes found in the lungs rather than in the liver. Kettle observed a remarkable case in which the lungs were so closely studded with minute metastases that the naked eye appearance was indistinguishable from miliary tuberculosis. Microscopically the carcinomata of the

FIG 161 Annular carcinoma of the colon causing stricture. There is hypertrophy of the muscle coat above the growth.

large intestine may range from well-differentiated adenocarcinomata, some mucus-secreting, to anaplastic spheroidal cell carcinomata. Classifying rectal carcinomata according to the degree of spread found at the time of operation Dukes [1] finds that the survival rate on a five-year basis for type A cases is 93 per cent., for B cases 65 per cent., and for C cases 23 per cent.

Vermiform Appendix. Tumours of the appendix apart from carcinoids are rare. Adenomata and benign connective tissue tumours

[1] Dukes, C. E, *J Path. & Bact.*, 1940, 50, 527.

have been described and may cause intussusception; **endometriosis** of the appendix may occur

Carcinoids or argentaffin tumours are by no means uncommon, being found in about 0·5 per cent. of all appendices removed at operation,

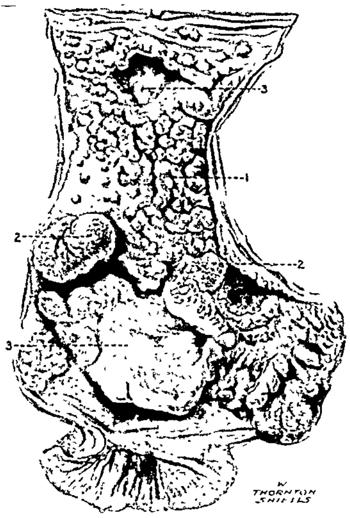

FIG 162. A rectum showing numerous polypi (1), villous papillomata (2), and two carcinomata (3).

but they are frequently small and may only be discovered on microscopic examination; they are generally observed in appendices showing fibrosis and are commonly found in association with other signs of neuromuscular hyperplasia such as luminal obliteration and neuromata; they are usually in the distal portion of the appendix and may be recognised as bright yellow nodules. Argentaffin tumours of

the appendix very rarely metastasise and much of the evidence would support Masson's [1] view that they are of blastomatoid nature associated with disturbances of the neuromuscular complex of the appendix rather than true tumours.

True carcinomata of the appendix are exceptionally rare and there is little doubt that the vast majority of cases reported as carcinomata are in reality argentaffin tumours.

Secondary tumours of the intestine are comparatively rare. The bowel is more commonly involved in the local spread of an adjacent growth, and transplantation occasionally takes place on to the mucous membrane of detached fragments from tumours higher up on the alimentary tract. The peritoneal surface is commonly infiltrated by secondaries seeded throughout the peritoneal cavity.

THE LIVER

Primary tumours of the liver are much less common than secondary metastatic growths, but several varieties, both innocent and malignant, may occur.

Innocent Tumours. The commonest tumour of any kind is the **angeioma.** This is usually of the cavernous type, and though included by custom among the blastomata, is probably a blastomatoid formation, arising by dilatation of existing capillaries and secondary hyp rtrophy of their walls (p 186). The tumours are frequently multiple, and are more common in old people than in young: they may grow to a considerable size. **Fibromata, lipomata,** and **myxomata** have been described, but are extremely uncommon.

The **adenoma** is uncommon. There are two types, one growing from liver cells, the other from the lining cells of the biliary capillaries; the former is the more common. The **liver-cell adenoma** forms a lobulated, nodular growth having a whitish colour; it is firmer than the surrounding parenchyma, and its limits are clearly defined. It is composed of cells closely resembling those of the normal organ, but having no regularity of arrangement, and exhibiting a good deal of variation of size and shape; they may be multinucleated, and they often contain bile. It is difficult to distinguish histologically between the compensatory hyperplasias which accompany fibrosis in the late stages of subacute hepatitis, and the liver adenomata, but there is no doubt that most if not all of the examples of multiple adenomata which may be encountered are instances of a reactive hyperplasia.

[1] Masson, P, *Am. J. Path*, 1928, **4**, 181, *id.*, 1930, **6**, 217, 409.

The **bile-duct adenoma** is a firm, rounded tumour which is often cystic. It is composed of tubules lined by columnar epithelium and supported by a fibrous stroma.

Malignant Tumours of the liver are comparatively rare in European

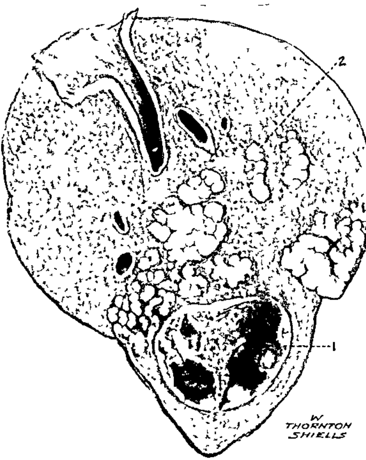

FIG. 163 Carcinoma of the liver. The primary tumour (1) is hæmorrhagic and bile-stained The secondary nodules (2) have a lobulated structure and closely resemble areas of regenerated liver tissue

countries, but in the East form a high proportion of cancers : carcinomata are more common than sarcomata.

Sarcomata[1] have been described, but it is probable that in the majority of cases they are either anaplastic carcinoma, metastic tumours, angeioendothehomata or in children teratoblastomata.

Primary **melanomata** have been described, but these tumours are more likely to be secondary than primary.

[1] Sheehan, H. L., *J. Path. and Bact*, 1930, **33**, 233

Carcinomata. Primary carcinoma of the liver is not very common and when it does arise it does so most frequently in a fibrotic (cirrhotic) liver. Fibrosis of the liver is usually secondary to destruction of liver cells, either in large irregular areas or in small but widely distributed foci. The surviving liver cells multiply and produce a nodular regenerative hyperplasia. In an advanced example the greater part of the liver is made up of regeneration nodules. Normally these nodules retain their non-tumorous nature, but in a few cases they become tumorous. In most of the fibrotic livers in which this change takes

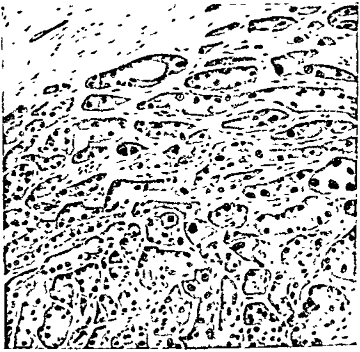

FIG. 164 Microscopic section of a primary liver-cell carcinoma In their form and arrangement the tumour cells closely resemble the normal liver cells.
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place a single regeneration nodule or a small group of them become carcinomatous In other livers, although one group may show the most pronounced change there may be multiple foci of carcinomatous change. Sometimes as a still greater rarity a carcinoma having similar histological features and a nodular distribution may arise in a liver free from fibrosis. The histological picture of the carcinomatous part generally shows columns of polygonal cells with well-formed nuclei very like the normal liver cells. The cells, however, vary in size and shape; some are much smaller than normal liver cells, others are much larger and others are multinucleate giant cells. The general appearance may not only be like the normal, but in some tumours there

is secretion of bile both in the primary and their metastases. The least malignant in spite of local invasion do not metastasise, others metastasise to the peritoneal cavity and the more malignant metastasise to the lungs and may produce secondaries all over the body.

The next commonest carcinomata of the liver arise from bile ducts in the liver and are therefore intrahepatic bile duct, tubular, cubical or columnar-celled adenocarcinomata.

Endotheliomata. These tumours are very uncommon and range from the angeioendotheliomata and tumours derived from Kupffer cells to

FIG. 165. Microscopic section of a bile-duct carcinoma of the liver. The tumour consists of irregular acini lined by cubical or low columnar cells, the structure being that of an adenocarcinoma. There is an abundant fibrous stroma. Groups of liver cells can be seen at the right hand side of the figure (1).

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complex reticuloendotheliomata showing both angeio-formative and hæmopoietic properties. They have been well reviewed by Ross [1] and Blondel.[2] It is possible that some of the tumours described as primary chorion-carcinoma of the liver in reality belong to this group. Ross's case was remarkable in that it arose in relation to a radium needle which had been accidentally implanted in the liver.

Adrenal-rest Carcinoma. This tumour is extremely rare, though some four or five examples have been recorded. Its importance in

[1] Ross, J. M., *J. Path. and Bact.*, 1932, 35, 609.
[2] Blondel, E., *Le tissu réticulo-endothélial du foie et ses tumeurs malignes*, Paris, 1933.

connection with the origin of the "hypernephromata" in general is elsewhere discussed (p. 261). It must be remembered that there may be a very close resemblance between the cells of a liver-cell carcinoma and the clear vacuolated elements we associate with a hypernephroma.

Secondary growths in the liver are very common in malignant disease of all kinds. They are particularly common in carcinoma arising in stomach, colon or rectum, presumably because the venous return from these organs is by the portal vein. Metastases by the hepatic artery from such organs as breast and bronchus are also very common. In addition to carcinomas of all kinds sarcomas freely metastasise to the liver.

THE GALL BLADDER AND BILE DUCTS

Innocent Tumours. Innocent connective-tissue tumours are rare.

Fibromata, lipomata, and **myxomata** have been known to occur.

Papillomata and **cystadenomata** are somewhat more common, especially in the region of the ampulla of Vater.

Malignant Tumours. Sarcomata are extremely rare.

Carcinoma is not uncommon. It occurs in the gall bladder, at the junction of the hepatic ducts, and in the ampulla of Vater. A large proportion of the cases are associated with the presence of gallstones. The tumour is usually an adenocarcinoma ; in the ampulla it has often a villous or papillomatous structure.

A well-recognised form of growth in the gall-bladder is the squamous carcinoma, and these are also met with it in the common bile duct ; it is generally regarded as an instance of metaplasia. Carcinomata of the gall bladder tend to invade the liver at an eary stage.

THE PANCREAS

Innocent Tumours. These are rare and seldom give rise to any symptoms. **Adenomata** and **fibro-adenomata** may occur as small nodular tumours. One form of pancreatic cyst is a true blastoma, being a **papillary** or **multilocular cystadenoma.**

Malignant Tumours. Sarcomata are very rare ; they are usually of the round-celled type.

Carcinoma. These tumours may arise from the glandular tissue or from the ducts and it is not always easy to decide which is the source in any given tumour. The tumours arising from ducts are usually

tubular, cubical or columnar celled and those from parenchyma solid acinar polygonal celled. But less well differentiated and mixed forms are sometimes found.

Tumours of the Islets of Langerhans. In common with tumours of other glands of internal secretion some of the tumours of the islets of Langerhans produce an internal secretion. The tumours may be adenomata or adenocarcinomata, they may be single or multiple and their cells may be polygonal, cubical or columnar arranged as solid trabeculæ or tubes. Most of them in some part resemble islets and some of their cells give similar staining reactions to those given by islets cells.

Ectopic pancreas may be found in the pyloric part of the stomach, small intestine or in a Meckel's diverticulum and pancreatic tumours may arise in any of these situations.

THE NERVOUS SYSTEM

THE MENINGES

Innocent Tumours. **Fibromata** and **lipomata** are rare tumours which may spring from any part of the dura mater or the pia-arachnoid, particularly in the mid-line over the corpus callosum, tuber cinereum or mid brain.

Osteomata occur as flat plaques in the falx cerebri and the tentorium, and also in the spinal dura mater. They are probably not blastomata, but are instances of metaplastic ossication.

Chondromata occur as small soft tumours attached to the membranes at the base of the brain.

Chordomata arise from remnants of the notochord in the region of the basisphenoid or basiocciput. Other very rare benign tumours are **cholesteatomata** and **dermoid cysts.** A **cavernous angeioma** is sometimes encountered in connection with spinal membranes **Cirsoid aneurysms** and **capillary telangiectases** which may be found in the meninges are not true tumours ; **angeiomata** either over the brain or spinal cord are very rare.

Meningeiomata are the most important tumours growing from the membranes These have been treated of in a previous chapter (p. 171), and little more need be said here. They probably arise from arachnoid villi and form nodular tumours or flat plaques of growth They are usually innocent, but may behave as malignant tumours infiltrating bones of the skull and even the brain They are liable to undergo degenerative changes

Malignant Tumours. Sarcomata. These tumours are rarely found in the meninges.

NERVE ROOTS

Neurilemoma (Schwannoma) (p. 175) may arise from nerve roots, particularly from the seventh, eighth and pars intermedia, when it is often known as an acoustic nerve tumour.

They are usually solitary, sometimes bilateral and sometimes form part of a general neurofibromatosis. Their microscopic appearances usually conform to similar tumours arising elsewhere (p. 176). They are liable to xanthomatous degeneration and in some of them, in addition to the usual cells, astrocytes are found.

Glioma of the optic nerve and neurocytoma of the Gasserian ganglion of the fifth nerve may be found.

BRAIN AND SPINAL CORD

The majority of the tumours of the brain and spinal cord have been described in Part II under the heading "Tumours of Nervous Tissue."

Angeiomata. The only angeiomata that are at all common are capillary hæmangeiomata or hæmangeioendotheliomata. They are usually small firm tumours having a pale yellow ochre finely porous cut surface They are commonest below the level of the tentorium and are usually found in the wall of a cyst. Although they are much rarer they may occur in the cerebrum. Histologically they consist of a close meshed network of fine capillaries surrounded by varying numbers of endothelial cells, histiocytes and xanthoma cells.

Pineal Tumours. These tumours, though uncommon, have a special interest because of the evidence they may provide for or against the idea that the pineal gland contributes an internal secretion. In some of the patients that develop a pineal tumour before the age of puberty there is evidence of mental, physical and sexual precocity. Since centres in the neighbourhood of a pineal tumour will be affected by pressure it is possible that the symptoms may be produced by this involvement and not by a secretion from the tumour. Many of the tumours arising in children have proved to be teratomas containing squamous epithelium, hair follicles, bone, cartilage and fat.

The more typical pinealomas are composed of pineal parenchyma cells, lymphoid cells, neuroglial cells and connective tissue stroma. In individual tumours the proportions of these cells vary. The most

characteristic is of sheets and strands of polygonal cells with abundant protoplasm and well-formed round nuclei ; surrounding the sheets are smaller deeply staining cells resembling lymphocytes and the whole

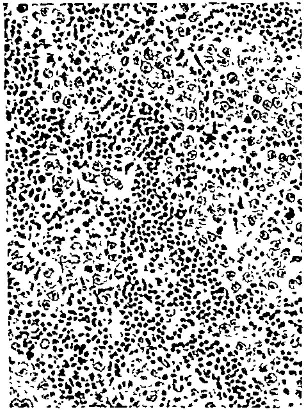

FIG 166 Pineal tumour composed of polygonal cells and groups of round cells resembling lymphocytes

tumour containing a varying amount of fibre. It has been suggested by D. S. Russell[1] that the majority of "pinealomata" are teratomata.

THE PERIPHERAL NERVES

The specialised tumours of the peripheral nerves have been described in a previous chapter (p. 174), and apart from these, tumours both benign and malignant are extremely rare. Neuroepithelioma has been described and Masson has described a curious rhabdomyoma.[2] Occasionally papillomata, lipomata and melanomata are observed with a definite nerve pattern distribution.

[1] Russell, D. S., *J. Path and Bact*, 1944, 54, 145.
[2] Masson P., and Martin, J. F., *Bull. de l'assoc p l'Étude du cancer*, 1938, 27, 1.

Secondary Tumours. Although it is common to find invasion of perineural lymphatics on microscopic examination of many tumours, actually distant metastases in nerves are very rare.

THE EYE

With two notable exceptions, the tumours of the eye are not of any particular interest to the general pathologist. **Fibromata, lipomata,** and **papillomata** sometimes grow from the conjunctiva, and **squamous-celled carcinomata** and **spindle-** and **round-celled sarcomata** may also be met with in this situation. The lacrymal gland may be the seat of benign or malignant tumours. Adenomas resembling the mixed salivary gland tumours occur, as do carcinomata and sarcomata.

The **neuroepithelioma** originates in the retina ; it is a soft hæmorrhagic tumour, and is highly malignant. Superficially, it has the characters of a round-celled sarcoma, but on close examination the cells are seen to be arranged in rosette form around a central lumen, the cell membrane bordering the lumen shows blunt processes protruding inwards, in abortive attempts to form rods and cones ; there are no cilia or blepharoplasts. It is a highly malignant tumour of childhood infiltrating the meninges A high proportion of the cases show a familial incidence and a study by Waller [1] would suggest that there is an inherited abnormality of the retina which is liable to undergo malignant change.

Malignant melanomata are derived from the pigmented cells of the choroid coat and more rarely from the iris and ciliary body. They project into the posterior chamber as rounded tumours of a dense black colour, and are mostly of the spindle cell type closely resembling the melanomata of the meninges. They disseminate widely, and are especially likely to form secondary deposits in the liver.

THE URINARY SYSTEM

THE KIDNEY

Innocent Tumours. The innocent connective-tissue tumours are usually small, though they are often multiple, and although they are common, they are seldom of any clinical importance.

Fibromata occur in the pyramids, where they form small round tumours, often enclosing one or two tubules in their substance ; very

[1] Waller, C. V., *Cancer Research,* 1941, 1, 517.

occasionally they are found under the capsule. A few examples of fibromata so large as to give rise to symptoms have been recorded. **Lipomata** are usually found under the capsule or in the substance of the cortex; they are often combined with a varying amount of fibrous tissue. They are nearly always quite small, but they may reach a considerable size. **Leiomyomata**, or, more commonly, **fibroleiomyomata**, occur as small tumours growing from the capsule. **Angeiomata** have been described as growing to some size in the cortex of the kidney. As a rule they are very small and are really capillary telangiectases; they are situated at the apices of the pyramids, and may give rise to very severe hæmorrhage. **Myxomata, chondromata,** and **osteomata** have been mentioned as occurring in the kidney, but they are so excessively rare that they may be disregarded.

The innocent epithelial neoplasms form an interesting study from the light they throw on the more important malignant tumours. Small white or yellowish tumours are quite common on the surface of the kidney, especially in the contracted granular organs. Some of them are **adrenal rests**, but the greater number are derived from the renal tubules. The majority are quite insignificant, but large adenomata may occasionally be encountered. Three types may be distinguished: (*a*) the **simple tubular adenoma**, (*b*) the **papillary cystadenoma**, and (*c*) the **solid acinar adenoma**. The last-named forms a rather larger tumour, and is of a darker colour; it is composed of small spheroidal cells lying in a somewhat loose fibrous stroma.

A **villous papilloma** may grow from the pelvis of the kidney, and is frequently the cause of serious hæmorrhage.

Malignant Tumours. Sarcomata. The pure sarcoma is not a common tumour in the kidney, though it may occur at any age. It is usually of the round- or spindle-celled variety; leiomyosarcomata may also occur.

Hypernephromata (Grawitz tumour). This is the commonest malignant tumour of the kidney. Nothing can be said to justify the term "Hypernephroma" except that it has become so embedded in medical terminology that its omission might be more confusing than its retention.

It is used for a group of tumours that have such characteristic features and that have been the subject of so much controversy that a detailed description of them appears to be justified.

The renal hypernephromata usually occur between the thirtieth and fiftieth years; they may arise in any part of the cortical tissue of the kidney, about an equal number of cases starting in the upper and

Secondary Tumours. Although it is common to find invasion of perineural lymphatics on microscopic examination of many tumours, actually distant metastases in nerves are very rare.

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THE URINARY SYSTEM

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It is used for a group of tumours that have such characteristic features and that have been the subject of so much controversy that a detailed description of them appears to be justified.

The renal hypernephromata usually occur between the thirtieth and fiftieth years ; they may arise in any part of the cortical tissue of the kidney, about an equal number of cases starting in the upper and

lower poles, and a rather higher proportion in the middle zone. The tumours are spherical in shape ; they project to a considerable extent

FIG 1

above the limits of the kidney, and their surfaces are often nodular. On section they are seen to be surrounded by a well-marked capsule of condensed renal tissue, but the growth has a tendency to burst through this capsule and form daughter nodules, which, in turn, themselves

become encapsuled. In time, almost the whole of the kidney may be invaded, and at quite an early stage the growth may extend into the pelvis. In advanced cases extension may also take place into the renal vein, and columns of growth mingled with blood clot may reach into the inferior vena cava.

The naked-eye appearance of a hypernephroma is very characteristic, and renders it possible to make a diagnosis from a macroscopic examination in a high proportion of cases.

In typical examples there is a primary encapsuled tumour surrounded

FIG 168. Microscopic section of a hypernephroma of the kidney The tumour cells are clear and vacuolated, and have a trabecular arrangement (1) The tumour is traversed by coarse strands of fibrous tissue (2).

Obj 16 mm apochrom Comp oc 4. Tube length, 160 mm.

by daughter tumours, which diminish in size as the limits of the growth are approached. Unaltered areas of tumour tissue are of a yellowish colour, but the cut surface has usually a mottled, deeply hæmorrhagic appearance, for the growths are exceedingly vascular, and there is nearly always an extensive extravasation of blood (Fig. 167). Central cystic degeneration of the larger nodules may occur, but more commonly there are areas of mucoid degeneration mingled with zones of dense fibrosis, the appearance as a whole suggesting very strongly the presence of cartilage.

The *microscopic* structure is of great interest. The tumour cells are cuboidal in shape, but they are liable to become distorted as the

result of mutual pressure; sometimes they are distinctly columnar. They have a small, round, deeply staining nucleus, and are distinguished by the clear, vacuolated appearance of their cytoplasm, an appearance

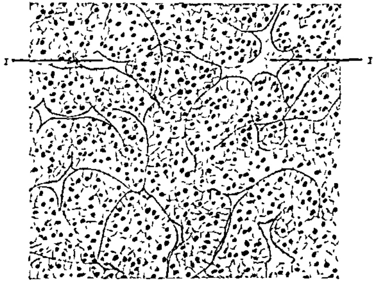

FIG. 169. Microscopic section of a hypernephroma of the kidney, showing a solid, trabecular type of growth, and close relationship of the tumour cells to the large capillary vessels (1).

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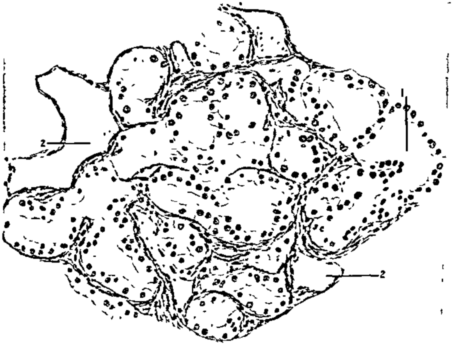

FIG 170. Microscopic section of hypernephroma of the kidney showing a tubular type of growth The drawing was made from another part of the same section illustrated in Fig 168 (1) Tubule lined with cubicle cells, (2) large capillary blood vessels.

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due partly to hydropic distension, partly to the solution, in the process of preparation, of the fat and glycogen present in the fresh state. Their arrangement is extremely variable.

Trabeculæ or solid alveoli are common (Fig. 168), and the latter may exhibit a lumen from the degeneration of the central cells. In some tumours there is a true acinous formation (Fig. 170), and in others the cells are often disposed in a papillomatous manner around a vascularised connective tissue core (Fig. 171). Occasionally cystic spaces, which may be partly filled up by an ingrowth of the lining cells, are formed, and every now and again the cells may be loaded with pigment granules, probably as the result of old hæmorrhages.

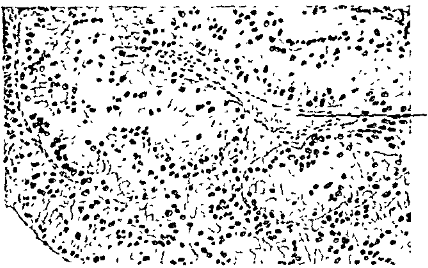

FIG. 171 Microscopic section of a hypernephroma of the kidney showing the papillomatous arrangement of the columnar tumour cells around a blood vessel (1).

Obj. 8 mm. apochrom Comp. oc. 4 Tube length, 160 mm

Except in the older parts of the tumour the stroma is always extremely scanty, and the groups of cells are separated by, and rest upon, delicate capillaries which consist of little more than tubes of endothelium (Fig. 169). The vascular supply is always abundant, and the capillaries are often dilated into large sinusoids.

Clinically, the renal hypernephromata give rise to very few symptoms, the most common being recurrent attacks of hæmaturia, often after some unusual exertion, and a varying amount of backache. For the most part the growth appears to be slow, and the formation of secondary deposits is delayed, so that, although the perinephric tissues are usually invaded and adherent to the tumour, a complete removal offers

a fair prospect of a cure. Cures have been recorded even when at operation tumour has been removed from that part of the renal vein not removed.

When dissemination does take place, the secondary deposits are prone to appear in the lungs and in bones. The lymphatic glands may also be affected and cases with a hitherto unsuspected hypernephroma have been diagnosed by an examination and the demonstration of metastases in an enlarged lymphatic gland. Sometimes the first clinical symptom is due to the appearance of a metastasis in some distal part of the body, such as bone. The histological picture is usually so faithfully maintained that a diagnosis of the primary can be made with reasonable assurance.

There has always been a considerable divergence of opinion as to the nature of the renal hypernephromata, but their renal origin is now generally accepted. Formerly, they were described under a variety of names, lipoma, sarcoma, angeiosarcoma, carcinoma, and endothelioma ; but in 1883 Grawitz demonstrated the presence of " rests," or misplaced fragments of suprarenal tissue on the surface of the kidney, and suggested that the origin of these tumours should be sought for in them.

It was an attractive theory, and immediately became popular. Nevertheless it did not receive universal acceptance, but was, from time to time, subjected to damaging criticism.

Put briefly, the argument in favour of the origin of the hypernephromata from misplaced fragments of the suprarenal gland is as follows. Such " accessory adrenals " are known to occur with some frequency : they are particularly common on the surface of the kidney (Fig. 172), and may also be found in the liver and on its under surface, in the retroperitoneal tissue along the course of the spermatic and ovarian vessels, in the broad ligament, and in the spermatic cord. That such " rests " should be the subjects of atypical cellular proliferations is quite a reasonable supposition, and one well in accord with Cohnheim's theories. The tumours themselves, with their bright yellow colour, closely resemble adrenal tissue ; and the histological structure, the trabecular arrangement of the clear vacuolated cells, is very similar to that of the zona fasciculata of the suprarenal gland. That the cells of hypernephromata contain fat and glycogen was also considered to be a strong point in favour of their origin from adrenal tissue ; but both these substances may be present in other neoplasms, and this argument, therefore, carries little weight.

So far, a strong case would seem to have been established, but a

more critical consideration raises very cogent doubts as to the validity of the conclusions which have been arrived at.

In the first place, Why is it so rare to find hypernephromata anywhere except in connection with the kidney? Instances have certainly been recorded of such extrarenal tumours in the liver and the broad ligament; but whereas hypernephromata are quite common in the kidney, very few investigators have had the good fortune to encounter them elsewhere. It may be objected that the "rests" occur in the

FIG. 172. Microscopic section of an adrenal "rest" on the surface of the kidney. The "rest" (1) is separated from the kidney tissue (2) by the kidney capsule (3). At (4) is a small adenomatous nodule.

Zeiss Obj. aa. Comp. oc. 4. Tube length, 160 mm.

kidney with much greater frequency than in other situations, but there is very little positive evidence in support of this contention, for it must be remembered that the surface of the kidney is examined practically always at an autopsy, while the broad ligaments and the spermatic cords are subjected to a much less searching scrutiny. With regard to the kidney itself, a systematic examination of all the cortical tumours, even to those of the minutest size, encountered throughout a fairly extensive post-mortem experience, has shown that only a small proportion of them consist of misplaced adrenal tissue; by far the greater number are primary kidney adenomata. From the anatomical

relations of the kidney and the suprarenal gland one would expect to find the majority of the hypernephromata in the upper pole of the kidney were they derived from adrenal rests; but, as we have seen, *this is not the case. Similarly,* the small whitish or yellow tumours found on the surface of the kidney, and usually termed "adrenal rests," may occur in any part of the organ.

Again, a suprarenal rest on the surface of the liver can scarcely escape notice in the course of an ordinarily careful examination, but *they are rare. So that, while fully acknowledging the occurrence of* such rests, especially in relation to the kidney, it seems probable that their frequency has been somewhat exaggerated.

A histological study of hypernephromata reveals several points of difference between the structure of these tumours and that of the adrenal glands.[1] In the hyperplasias and neoplasms of the latter a solid structure is the rule; one never sees a papillomatous formation, and only rarely is there any suggestion of the production of acini or tubules, whereas both of these are common enough in the hypernephromata. Further, there is a very striking likeness between many of the malignant renal tumours and the small adenomata so often found on the surfaces of granular kidneys. From a consideration of the histological features, therefore, one is forced to the *conclusion that the so-called hypernephromata are really renal in* origin.

Opinions are again divided on the question whether the tumours arise from mature kidney cells, or from rests of embryonic renal tissue. Stoerk [2] holds that they are derived from adult renal tubules in which the "tissue tension" has become disorganised as the result of a local or generalised chronic atrophic nephritis. Wilson [3] has approached the problem from the embryological point of view. While he believes that the hypernephromata arise in embryonic rests, he regards these rests as representing undeveloped areas of the kidney anlage, and not misplaced fragments of the suprarenal gland.

Nicholson [4] in an exhaustive and convincing paper strongly supports Stoerk's views. He concludes that "the hypernephromata of the kidneys arise in the renal epithelium. No instance has been described whose origin in suprarenal tissue, assumed by Grawitz, is assured." More recently Newcomb [5] has studied the problem with great care and

[1] Glynn, *Q. J Med*, 1911–12, 5, p 157
[2] *Ziegler's Beitrage*, 1908, 43, 393
[3] Wilson and Willis, *Journal of Medical Research*, 1911, 24, 73
[4] Nicholson, G W., *Guy Hospital Reports*, 1923, 73, 164.
[5] Newcomb, W. D, *Proc. Roy. Soc Med.*, 1936, 30, 113.

produced strong morphological evidence in support of a renal origin for hypernephromata.

Tumours of the adrenal cortex itself are rare. Small nodular hyperplasias, or adenomata, are by no means uncommon, but malignant growths, or innocent tumours of any size, are seldom found—a fact of some significance in view of the preceding argument.

Adrenal carcinomata are very much more malignant than the corresponding tumours of the kidney ; they may be bilateral They grow rapidly, invade lymphatic glands at an early stage, and are usually fatal in spite of operative measures.

A very interesting feature is the association of these tumours with the development of abnormal sex characters. Female children and women before the menopause tend to develop certain male sex characters, while boys show sexual precocity. Adult males are unaffected. The renal hypernephromata have never any effect on the sexual characters of the patient. It is true that renal hypernephromata are very rare in children, but they are not uncommon in adult females, and the fact that they are never associated in these patients with abnormal sexual characters is a strong argument against Grawitz's hypothesis.

It is probable that the tumours described as primary hypernephromata of the liver and elsewhere are in reality neoplasms of those organs which have undergone degenerative changes thus producing a " hypernephromatous " appearance.

It is difficult if not impossible to draw any sharp distinction between the renal hypernephroma and renal carcinoma, yet they are tumours more infiltrative than the hypernephroma and lacking the characteristic yellow colour which on microscopic examination are seen to be adenocarcinoma or papillary cystadenomata.

The pelvic tumours are **transitional-celled carcinomata ;** very occasionally they may be of the **squamous-celled type,** exhibiting prickle cells and keratinisation. A **malignant papilloma** may occur. The pelvic carcinomata very often develop as a late result of the chronic irritation of calculi

Teratoid Tumours. The mixed sarcoma (Wilms' tumour) of infancy appears, as its name implies, in early childhood. It has been described in the section on teratomata (p. 202).

Secondary tumours of the kidney are not common except as a late phenomenon. The growth may reach the organ by direct extension, by the peri-ureteric lymphatics, or by the blood stream.

THE URETERS

A few rare tumours of the ureter have been described, such as a primary **transitional-celled carcinoma**, and an **adenoma**, presumably derived from Wolffian remnants. The only neoplasm of any importance is the **villous papilloma,** which may grow at the upper or the lower extremity of the tube, projecting either into the pelvis of the kidney or into the bladder.

THE BLADDER

Innocent Tumours. Fibromata, myomata, and **fibromyomata** are all rare tumours ; they tend to become pedunculated. **Myxomata** have been described, but are probably merely fibromata which have undergone myxomatous change. **Adenomata** arising from mucous glands may very occasionally be encountered at the base of the organ

FIG. 173. Urinary bladder opened to show numerous villous papillomata springing from the mucous membrane.

The commonest tumour of all is the **villous papilloma.** This tumour is frequently multiple, and is much more often seen in men than women. It forms a soft friable growth of a pinkish colour, and consists of a collection of delicate villous processes attached to the mucous membrane by a connective-tissue stalk (Fig. 173). When the tumour is floated out in water, the appearance is not unlike that of a certain type of seaweed. *Microscopically*, the growth is composed of delicate connective-tissue stalks, each containing a central blood vessel and being covered by a stratified epithelium (Fig. 44).

Although the tumour is usually innocent, it must always be regarded with suspicion for the following reasons: it spreads widely by direct transplantation over the surface of the viscus; it tends to recur after removal, since minute outlying tumours may easily be overlooked; and it is often extremely difficult to determine its nature from a histological examination, for an apparently innocent growth may infiltrate its stalk and invade the bladder wall.

Malignant Tumours. Sarcomata of the bladder form sessile, fleshy tumours which may be multiple; they are rare, but may occur at any age. An interesting tumour which may be encountered is the rhabdomyosarcoma.

Carcinoma. Several varieties of carcinoma of the bladder may be recognised. The malignant papilloma forms a friable, cauliflower-like tumour which projects into the cavity of the viscus; at the same time there is a diffuse infiltration of the bladder wall, the tumour having the structure of a transitional-celled carcinoma, or a carcinoma simplex. Sometimes the tumour forms a slightly raised plaque of growth, and this type may be distinctly scirrhous, possessing a large amount of fibrous stroma. Tubular columnar celled carcinoma sometimes mucus-secreting, may arise either at the apex or base of the bladder. In either of these situations patches of columnar epithelium may be found apart from tumours. An interesting variety is that associated with the presence of the bilharzia ova. In response to the irritation of the ova, the epithelium undergoes a dense nodular hypertrophy which may involve the ureter and renal pelvis and a squamous carcinoma may eventually develop. Mention has been made (p. 40) of the occurrence of carcinoma of the bladder in aniline workers.

Secondary Growths. The bladder frequently becomes involved in malignant growths of the rectum and the prostate in the male, and of the uterus in the female. In general peritoneal dissemination secondary tumours may be situated on the fundus.

THE URETHRA

Tumours of the urethra are rare. Small fibrous polypi and **epithelial papillomata** are sometimes seen, chiefly in the anterior urethra. A polypoid **fibro-adenoma** occurs in the prostatic urethra. The **urethral caruncle** of women may be an angeioma, but is much more commonly an area of simple vascular granulation tissue.

Primary carcinoma is quite rare.

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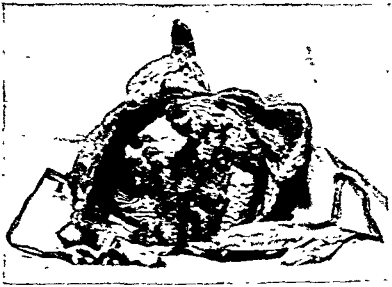

Fig. 173. Urinary bladder opened to show tumour as well as papillomata springing from the mucous membrane.

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Primary carcinoma is quite rare.

THE MALE GENITAL ORGANS

THE PENIS

Innocent Tumours. Papillomata occur with some frequency on the glans and prepuce. They form cauliflower-like excrescenses, which may reach a considerable size. The majority of them are to be regarded as irritative hyperplasias, due to the retained secretion under a tight foreskin, or to a venereal discharge.

Very rare innocent connective tissue tumours are the **fibromata, lipomata,** and **neuromata. Angeiomata** have been found in the corpora cavernosa.

Malignant Tumours. The commonest tumour is the **squamous-celled carcinoma.** This usually occurs as a malignant papilloma, but it may form a depressed ulcerated growth with a hard raised border. It appears somewhat late in life, and is frequently associated with phimosis. The majority of the tumours originate at the orifice or on the inner surface of the prepuce, but the glans is often primarily affected especially in the region of the corona. There is seldom any widespread dissemination, but the inguinal glands are frequently infected.

Sarcomata. Primary sarcoma of the penis is very rare, but, as in other cutaneous surfaces, **melanomata** may occur.

THE PROSTATE

Innocent Tumours. Fibromata, myomata, fibromyomata, and **adenomata** are potential tumours of the prostate, but it is doubtful if they often occur as true blastomata. A very common condition, however, is a diffuse hypertrophy of the organ in which all the elements entering into its composition participate. Simple enlargement of the prostate appears after the fiftieth year; it may be unequal and nodular, or diffuse throughout the gland.

It has been suggested that this condition is a hyperplasia associated with an endocrinal imbalance consequent on the male menopause and is comparable with chronic mastopathia of the breast.

Though there is overgrowth of both the fibrous and muscular constituents, the most marked change is in the glands These become elongated and dilated, and their epithelium may show a considerable overgrowth, though the individual cells retain their form. Concretions, known as corpora amylacea, are often present in the tubules (Fig. 174) The adenomatous hypertrophy may be diffuse throughout the gland,

or it may be peculiarly localised. In the latter condition small nodules, apparently possessing an independent growth, are present in different parts of the organ, and it is probable that we are not dealing with true multiple adenomata rather than with a blastomatoid process. It is not uncommon to find pure leiomyomatous nodules. It is difficult to deny the tumorous nature of these multiple myoadenomata first because they are localised and not distributed throughout the gland, and second because they are so atypical in their growth that the normal prostate forms a capsule around the mass. Prostatectomy as practised

FIG 174 Microscopic section of a simple hypertrophy of the prostate There is glandular hyperplasia, many of the dilated tubules containing corpora amylacea (1), there is also overgrowth of the muscular fibres (2), and small chronic inflammatory foci can be seen in places (3)

Obj. 16 mm. apochrom. Comp oc. 4. Tube length, 160 mm

at present would be impossible but for this capsule of prostate which remains after the operation.

Malignant Tumours. Carcinoma. This is probably more frequent than is generally supposed; some statistics show that 10 per cent. of all tumours of the prostate are carcinomatous The growth is an adenocarcinoma, consisting of small irregular acini lined by low columnar cells (Fig. 175). An encephaloid carcinoma simplex may also occur. As a rule, growth is somewhat slow, and dissemination is delayed; eventually, however, the bladder becomes invaded, and the aortic glands as high as the diaphragm become greatly enlarged with

secondary deposits. In some cases numerous metastases form in the bones in all parts of the body, and latent cases [1] only rendered apparent by their metastases are not uncommon.

Two features of peculiar interest in carcinoma of the prostate have recently been demonstrated. Both the normal and malignant prostatic epithelium elaborates a phosphatase which is active in an acid medium,

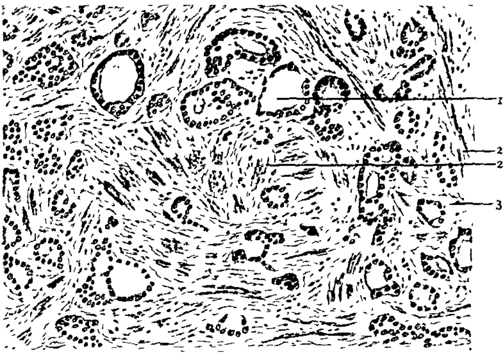

FIG. 175. Microscopic section of an adenocarcinoma of the prostate, showing (1) irregular carcinoma acini, (2) muscle bundles and (3) connective tissue stroma derived from the normal constituents of the gland

Obj 8 mm. apochrom Comp oc. 4. Tube length, 160 mm.

and the serum content of this acid phosphatase is sufficiently raised to be of diagnostic value in cases of carcinoma. The other feature is that by the use of diethylstilbœstrol, carcinomatous growths of the prostate have apparently been arrested and bony metastases have disappeared.

Sarcomata are rare, but any of the ordinary varieties may arise.

THE TESTICLE

Tumours of the testicle form a very difficult branch of pathology, and even now there is much confusion in respect to them. This is largely the result of the anatomical peculiarities of the gland, for a neoplasm growing in its substance has to overcome a very serious

[1] McGavin, D., *Brit. J. Surg.*, 1938, 25, 612.

mechanical obstacle in the stout tunica albuginea. The pressure exercised by this capsule results not only in impairment of nutrition and undue necrosis of the tumour, but also in a partial obliteration of those distinctive histological features which should help us in arriving at a correct understanding of its nature.

Innocent Tumours. These are so rare as to be of no consequence. **Fibromata** have been described but are probably blastomatoid processes and not true neoplasms **Myomata, chondromata,** and **osteomata** must be extraordinarily rare as simple tumours, though muscle, cartilage, and bone may be present in excess in the teratomata. There can be little doubt that the innocent chondroma of the text-books is really a teratoma (p. 84).

Malignant Tumours. Practically all the tumours of the testicle are actually or potentially malignant. They do not commonly occur before the age of twenty and are usually unilateral.

Though from the position of the gland one might expect the patients to seek medical advice at an early stage of the disease, the prognosis is not very favourable, for metastases seem to form in many cases before the primary tumour has attained such dimensions as to give rise to anxiety.

Ewing and others have held the view that all malignant tumours of the testicle are teratomata. In some the usual different types of cells can be identified, in others the whole mass appears to consist of only one type of cell. Other pathologists group the tumours under different headings. Undescended testicles show a particular liability to tumour formation.

Seminoma. This is the commonest form of malignant tumour and in the past was called a sarcoma. The tumours form masses of soft white tissue with little stroma or just sufficient to produce septa dividing the tumour into irregular lobules. They are vascular and liable to hæmorrhage or necrosis particularly in the central parts. Histologically they consist of close-packed masses of large polygonal spheroidal or small spheroidal well-formed cells. The cells have hyperchromatic nuclei having a dense chromatin net.

Teratomata. The next commonest form of malignant tumour shows sufficient differentiation of its cells to warrant a diagnosis of teratoma (p. 198). The tumours, however, vary from those in which the various tissues are easily identified to those in which one or other type predominates and the other tissues can only be identified after patient search. When the features of a teratoma are not apparent and the tumour is very cellular it is usual to include it under the heading of **Mixed Tumours.**

These will resemble the seminomas naked-eye, but under the microscope show more obvious epithelial cells often arranged in groups or forming tubes.

Chorion-carcinoma resembles the same tumour arising in the female except that in the testicle it is associated with a teratoma (p. 203).

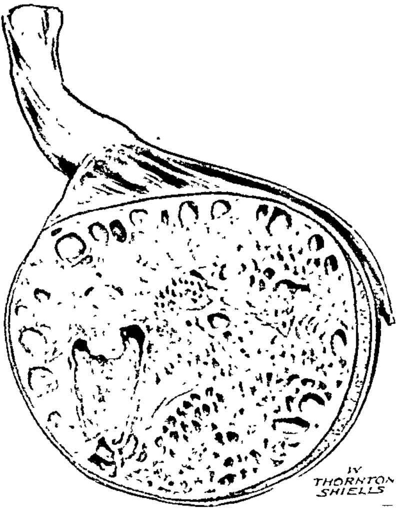

FIG 176 Teratoma (fibro-cystic disease) of the testicle.

The teratoma may be well formed or it may be largely destroyed by the tumour. Gonadotropic hormone may be excreted in the urine in chorion carcinoma or less commonly in teratomas of the testicle.

Interstitial gland tumours are rare, but both benign and malignant forms have been described. They consist of a parenchyma of polygonal cells with little interstitial tissue and a disorderly grouping in masses except when they are forming a pallisade along capillaries. The cytoplasm is usually intensely acidophilic, granular or vacuolated. The

nuclei are round, usually centrally placed in the cell and vary from pale staining small nuclei with a delicate chromatin net to hyperchromatic large nuclei with a dense mass of chromatin. In two cases recently described by Bonser and Hawksley [1] the tumours were both smooth on cut surface and of a definite pale brown colour.

Other tumours of testicle have been described, such as sarcomata, hypernephromata and endotheliomata, but their differentiation from the teratomas and mixed tumours is at present very difficult

Ectopic adrenal tissue is sometimes found in the spermatic cord and epididymis and very rarely may become tumorous.

THE FEMALE GENITAL ORGANS

THE EXTERNAL GENITALIA

Innocent Tumours. Fibromata usually grow in the labia majora; they tend to become pedunculated, and may reach a considerable size. **Myomata, lipomata,** and **angeiomata** are less common.

A **chondroma** has been described arising in the clitoris.

Adenomata or **Hidradenoma** [2] may arise in relation to sweat glands and have a characteristic appearance having a complex glandular pattern lying in a fibrous stroma; they have been mistaken for adenocarcinomata but are benign.

A rare tumour is an **adenoma** of Bartholin's glands.

Warty and papillomatous growths, blastomatoid in nature, are fairly common as a result of chronic infections of the genital tract.

Malignant Tumours. Sarcomata. These are not often seen, but the round- or spindle-celled forms may be met.

Melanomata are also rare, though they are rather more common than the pure sarcomata.

Carcinoma. This is a not unusual form of tumour and occurs as a nodular or papillary growth. It is of the squamous-celled variety, and ulcerates fairly readily. Metastases are found in the inguinal glands. An adenocarcinoma is also described as growing from Bartholin's glands.

THE VAGINA

Innocent Tumours. Simple **cysts** are not uncommon; they usually develop from the Wolffian or Gartner's ducts, and are always found in

[1] Bonser, G. M. and Hawksley, L. M., *J. Path and Bact*, 1943, **60**, 295.
[2] Rothman, D. and Gray, S. H., *Am. Journ. Obstet. Gynæc.*, 1939, **38**, 509.

the antero-lateral wall and may be lined with cubical or columnar epithelium, which may be ciliated, or by squamous epithelium. Vaginal inclusion cysts lined by squamous epithelium may occur in posterior or lateral walls. **Mucous polyps** are almost always of inflammatory origin. Polypoid **fibromata** and **myomata** may form large tumours, but they are rare, as are also **lipomata.**

Malignant Tumours. Sarcomata. These are not common, but the usual forms may be encountered. The vaginal sarcoma of children or botryoid sarcoma is histologically mesodermic and may consist of a number of connective tissues or undifferentiated cells.

Carcinoma. Primary carcinoma, though rare, may be seen in any part of the vagina, but most of the cases start at the external orifice or in the posterior fornix. It is of the squamous-celled variety, and forms either a papillomatous or a diffuse nodular growth.

Secondary Growths. The vagina is often involved in the growth of a carcinoma of the cervix uteri. In chorion-carcinoma deposits sometimes appear in the vagina, and may be the first manifestations of the condition.

THE UTERUS

Innocent Tumours. Pure **fibromata** and **myomata** are occasionally encountered, but the commonest tumour of the uterus is the **fibro-myoma** or leiomyoma (see p 93) ; indeed this neoplasm forms a large proportion of all the tumours met with in the female. Fibromyomata, or fibroids, are composed of interlacing bundles of smooth muscle fibres mixed with a varying amount of fibrous tissue, and form spherical or nodular tumours of a very dense consistence. They are practically always multiple, and may be situated in the substance of the muscle wall, when they are known as interstitial fibroids, or under the endometrium or the peritoneum, forming the submucous and subserous fibroids respectively ; in the last two situations they tend to become pedunculated. These tumours are subject to various retrograde changes, among which the fibrous, myxomatous, hæmorrhagic, necrobiotic, calcareous, fatty, and putrefactive degenerations may be mentioned. Occasionally, in a uterus the seat of multiple fibroids a sarcomatous change may be manifested in one or other of the tumours.

Adenomyoma (adenomyosis). In this condition the uterus may be slightly or greatly enlarged, though it never reaches the size sometimes found with fibromyomata. The enlargement is usually more or less symmetrical and unless associated with fibromyomata never nodular. The cut surface of a specimen shows that the enlargement is due to a

thickening of one wall usually or one wall mostly and slighter thickening of the opposite wall. The affected part has a whorled and trabeculated pattern of white fibres on a grey glistening background, sometimes very finely honeycombed and its outline is not sharply defined, the outer parts blending with the uterine muscle. It almost always involves part of the endometrium. In histological sections it consists of a blending of muscles and tubules lined by cubical or columnar epithelium. The tubules are scattered throughout the mass in some tumours and grouped into irregular aggregations in others. Sometimes rich cellular

FIG 177. Section of an adenomyoma of the uterus. The tumour is composed of interlacing bundles of smooth muscle fibres (1), among which lie gland tubules embedded in a cellular stroma (2)

Obj 16 mm. apochrom Comp oc. 6. Tube length, 160 mm.

fibrous tissue like that in the endometrium is found around the tubules. The tubules very rarely provide evidence of menstrual activity and even when they do it is minimal. Novak agrees with others that this is not a true tumour, but a benign invasion of the uterine musculature by endometrium He explains the absence of menstruation by assuming that it is of an unripe or immature variety. If Novak is right this is not a tumour, but an atypical endometrial hyperplasia.

Endometriomata are not true tumours, but fragments of ectopic endometrium which usually menstruate and the blood, having no outlet, accumulates to form various forms of blood cysts. They are commonest in the ovaries or peritoneum of the pelvis and may be found beneath the umbilicus, and rarely in peritoneum in other parts of the lower abdomen, in hernial sacs or in operation scars. They are probably

examples of abnormal peritoneal differentiation and are not true tumours.

Adenomata of the uterus occur as soft polypoid tumours springing from the endometrium. It may be difficult to be certain as to the nature of these mucous polyps, whether they should be regarded as true neoplasms or not, but it is probable that many of them are blastomatoid processes.

Malignant Tumours. Sarcomata [1] are rarer than carcinomata, and occur at an earlier age. Fibro-, myo-, and polymorphic-celled sarcomata may arise from the body of the uterus, and round-celled sarcomata from the endometrium.[2] The commonest is a sarcomatous charge in a leiomyoma (fibroid).

Mixed Tumours [3] are rare but of considerable interest as they should probably be classified as teratoblastomata. They may arise in the cervix or in the corpus, usually in the cornua and form gelatinous polypoid masses filling the uterine cavity and protruding from the cervix ; they may present as cervical polypi, and with small fragments of tissue it may be difficult to recognise microscopically their true nature. Microscopically they consist of stroma of loose anaplastic connective tissue with adenoid areas and zones of cartilage and muscle. The cervical group may occur in children (sarcoma botryoides), but those in the corpus usually arise about the menopause. They are extremely malignant, radio-resistant and are liable to recur locally even where a radical hysterectomy has been performed.

Carcinomata. Two types of malignant epithelial new growths are seen in the uterus, the carcinoma of the body, and the form arising from the cervix ; the latter is much the more common.

The cervical carcinoma may arise from the surface epithelium or from the cervical glands, and may be of the squamous-celled type or an adenocarcinoma ; a spheroidal-celled type also occurs. A rare form is the mucus-secreting adenocarcinoma which infiltrates deeply into the cervix, but may be extremely well differentiated histologically and difficult to distinguish from a chronic cervicitis with glandular overgrowth. It grows in three main forms, the papillary or cauliflower, the ulcerative, and the diffuse nodular. The growth remains localised in the pelvis for some time, though at a late stage metastases may occur in any part of the body. The broad ligaments and the bladder are often

[1] Novak, E and Anderson, D F, *Am J Obst and Gynæc*, 1937, **34**, 740

[2] Tudhope, S. R and Chisholm, A. E, *J Obstet. and Gynæc, Brit Emp*, 1934, **41**, 708.

[3] Liebow, A A and Tennant, R, *Am J Path*, 1941, **17**, 1, Simpson, E. E, *Arch of Path*, 1943, **36**, 535.

invaded quite early; later, extension takes place to the rectum, while involvement of the ureters gives rise to hydronephrosis and derangement of the renal functions, so that uræmia is often the immediate cause of death.

The local condition in an advanced carcinoma of the cervix is very terrible. Immediately inside the vulva is a foul cavity representing the bladder and the vagina; the recto-vaginal septum may also be destroyed, while of the body of the uterus only a small portion of the fundus may be left.

By far the largest number of carcinomata of cervix occur in women who have had a child, and it is impossible to exclude the possibility that previous damage to the cervix plays an important part in the production of this growth.

Carcinoma of the body of the uterus is an adenocarcinoma, and occurs as a localised papillary growth or as a diffuse infiltration of the whole of the endometrium, squamous-celled carcinoma may also arise either in an endometrium which has already become squamous or as the result of metaplasia in the tumour. It extends for a variable distance through the uterine wall, and may crop out on the peritoneal surface, but it is much less malignant than the squamous-celled cervical growth, and remains localised for a much longer period.

Chorion-carcinoma. This interesting tumour has already been described in the general section on the teratomata (p. 203).

THE FALLOPIAN TUBES

Innocent Tumours. Primary tumours of the Fallopian tubes are very rare. **Fibromata, myxomata, myomata,** and subserous **lipomata** may be met with, while of the epithelial neoplasms **papillomata** and **adenomata** may cause a considerable enlargement of the tube.

Malignant Tumours are even more uncommon, but a papillary and a diffuse **carcinoma** may both be seen. **Sarcomata** have also been described A **chorion-carcinoma** associated with an ectopic gestation is a rarity, but Kettle saw two cases, both rapidly fatal.

THE OVARIES

No classification of ovarian tumours is entirely satisfactory; the following agrees generally with that given by Novak.[1]

Innocent Tumours. The innocent tumours of the ovary may be

[1] Novak, E., *Gynæcological and Obstetrical Pathology*, London, 1940, p. 275

divided into two main classes, the solid and the cystic; both forms are frequently bilateral.

The cystic tumours are by far the commoner, and may be derived from a variety of sources. Though it would be more satisfactory to classify them according to their origin from the Graafian follicles, corpora lutea, Wolffian or parovarian remnants, or the germinal epithelium, this is often impossible, and we have to content ourselves with a recognition of morphological differences.

The majority of ovarian cysts are not neoplastic, being derived from an atretic follicle, but they are invariably unilocular and are of little clinical importance. The commonest neoplastic cyst is the **pseudo-mucinous cystadenoma** which may be unilocular or multilocular and *there may be areas in which a large number of small loculi give the* appearance of a solid nodule of tissue. The simple mucoid cyst may be unilocular or multilocular. Its wall is composed of fibrous tissue and is lined by a layer of columnar epithelium. The epithelium is very characteristic, being tall with a clear refractile cytoplasm; basal nucleus and goblet cells are not infrequent. Papilliferous outgrowths are unusual, but adenomatous areas formed by small loculi are not infrequent. The inner surface of the wall is smooth except for the presence of occasional low ridges which mark the positions of former divisions between separate loculi which have coalesced. The cysts are filled with the glairy fluid which is not precipitated by acetic acid, and is, therefore, not a true mucin. In a rare form of cyst the lining epithelium is distinctly ciliated.

Another variety of ovarian cyst is the **papilliferous serous cystadenoma** containing clear watery fluid rich in serum proteins. In this form the epithelial lining of the cyst wall shows a tendency to proliferation, so that small warty growths are formed which project into the cavity. This proliferation may be so extreme that the whole cyst becomes filled with a soft, semi-gelatinous growth. The character of the epithelium is much more variable than in the pseudomucinous cystadenoma and is not infrequently ciliated At times the cellular proliferation is so abundant that the solid growth bursts through the wall. When this occurs the tumour cells are liable to become seeded all over the peritoneum, and a condition results which is difficult to distinguish from true malignant dissemination. The confusion is still further increased by the fact that an undoubted malignant change may appear in the epithelium of a papillary cystadenoma. The cells approach the vegetative type, and the peritoneal deposits are definitely infiltrative in their growth.

Solid benign tumours of the ovary are comparatively rare, but **fibromata** and **myomata** both occur, the former being the commoner. These tumours are usually extremely dense and hard, but they may become softened from myxomatous degeneration, and pseudo-cysts are sometimes formed in this way. **Adenofibromata** [1] occur in which the surface of the ovary is covered with warty outgrowths and the solid

FIG 178 A section of a Brenner tumour showing the rests of epithelial cells in a mass of fibrous tissue.

tumours show a variable degree of cyst formation; the epithelium shows all the variability of germinal epithelium from cuboidal to ciliated columnar types.

The **Brenner tumour** [2] is a slowly growing tumour of moderate size developing after the menopause and having the naked-eye appearances of a fibroma save that it may be slightly yellowish in colour. Microscopic examination reveals a fibromatous overgrowth and lying in this are epithelial nests of polyhedral cells, extremely uniform and having a striking resemblance to squamous epithelium; there is marked

[1] Lepper, E. H., *Proc. Roy. Soc. Med.*, 1935, 28, 1645; Schiller, W., *Am. J. Path.*, 1943, 35, 391.
[2] Novak, E. and Jones, H. C., *Am. J. Obstet. and Gynæc.*, 1939, 38, 872.

the endometrium shows evidence of a marked decidual reaction of the stroma.

Arrhenoblastoma. This is a masculinising tumour and is associated with amenorrhea, sterility and breast atrophy and subsequently hirsuties and other signs of masculinisation, but no psychological

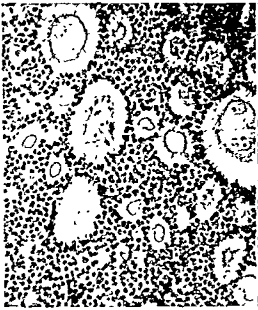

Fig. 179 Granulosa celled tumour: diffuse but with cells around spaces containing large ova like cells.

Fig 180 Granulosa-celled tumour: similar to Fig 179, but the cells are grouped in acini

Fig 181 Granulosa-celled tumour: partly acinar and partly diffuse.

change. Microscopically the tumours may consist of tubule formation closely resembling the infantile testis or solid cords of cells; interstitial cells may be present.

Adrenal Tumour of Ovary (Ovarian hypernephroma). The symptoms are similar to arrhenoblastoma, but the tumours are strikingly yellow and resemble cortical adrenal tissue microscopically. There is considerable debate as to whether these tumours are derived from ovarian adrenal rests or not.

Gynandroblastoma is a tumour with both clinical and morphological features of the granulosa cell tumour and arrhenoblastoma.

Dysgerminoma. This is a tumour without hormonal activity though a high proportion of cases have been described in which it has been associated with pseudo-hermaphrodism Microscopically it is almost identical with the seminoma of the testis, consisting of follicles of large pale cells with prominent nuclei lying in a stroma of connective tissue and small lymphocytes; foci of epithelioid cells are more frequent in the dysgerminoma than the seminoma and the tumour in the female is of a low grade malignancy in contrast to that of the male.

Luteoma. A true adenoma or a carcinoma may rarely arise from cells of a corpus luteum.

Secondary Growths. As Bland-Sutton and others have pointed out, the ovaries are frequently invaded by secondary growths from the breast or any of the abdominal viscera. Probably many of the malignant tumours of the ovary which are regarded as being primary in that organ are really metastatic growths, so that great care must be exercised to eliminate a primary focus elsewhere when dealing with what is apparently an ovarian carcinoma. The Krukenburg tumour of the ovary is a diffuse secondary carcinomatosis of the ovary, in which the infiltrating cells are spheroidal and show mucous secretion so that the nucleus is displaced to one side giving the cells a " signet ring " appearance The tumours are commonly bilateral and although the ovaries are considerably enlarged they maintain their normal shape and are solid, though somewhat gelatinous on the cut surface. The primary growth is usually in the gastrointestinal tract and very often a diffuse anaplastic carcinoma of the stomach of the " leather bottle " type

THE BREAST

Tumours of the male breast are merely pathological curiosities; a typical carcinoma may occur, and also some of the innocent tumours such as fibro-adenoma, but for all practical purposes we may confine

ourselves to a consideration of the neoplasms found in the female organ.

THE NIPPLE

The nipple itself is sometimes the seat of tumour formation.

Simple **papillomata,** tending to become pedunculated, are occasionally seen ; **angeiomata** are very rare, and so are **melanomata.**

A **squamous-celled carcinoma** may develop on the nipple, sometimes *supervening on a chronic inflammatory process.*

Paget's Disease of the Nipple. This is a condition of considerable importance, though most contradictory statements as to its nature

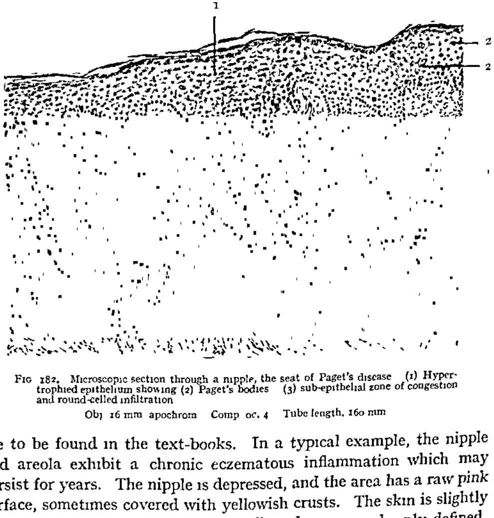

FIG 182. Microscopic section through a nipple, the seat of Paget's disease (1) Hypertrophied epithelium showing (2) Paget's bodies (3) sub-epithelial zone of congestion and round-celled infiltration

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are to be found in the text-books. In a typical example, the nipple and areola exhibit a chronic eczematous inflammation which may persist for years. The nipple is depressed, and the area has a raw pink surface, sometimes covered with yellowish crusts. The skin is slightly thickened, and the margins of the affected area are sharply defined. *Microscopically* (Fig 182), the change is seen to consist in a proliferation of the epithelium combined with desquamation, and a very dense, round-celled infiltration of the corium together with increased vascu-

larity. Here and there in the surface epithelium there are cells which may show a swelling and vacuolation of the cytoplasm, resulting in the formation of the "Paget bodies," which were at one time believed to be parasites Finally, Paget's disease of the nipple is almost invariably associated with a carcinoma simplex in the deeper parts of the breast, and the main interest of the condition lies in the possible relationship between the two processes.

According to the older theory the eczema of the nipple is the primary condition, and the carcinoma develops later as the result of chronic

FIG 183 Microscopic section through the skin of a breast in the region of the nipple, showing malignant infiltration (1) Surface epithelium, (2) carcinoma alveoli.
Obj 16 mm apochrom Comp oc 4. Tube length, 160 mm.

inflammatory changes, or, possibly, a direct infection, spreading down the ducts.

Sampson Handley suggested that the nipple condition is secondary to the carcinoma of the breast, and is due to changes depending on the obstruction of the lymphatic drainage of the part from permeation of the vessels by the cancer cells.

Muir [1] suggests that the Paget cells arise in an intraduct carcinoma and reach the skin by extension and infiltration from the duct, and adds that he has never seen a case of Paget's disease without intraduct carcinoma. Inglis [2] believes that the cells arise from cells at the junction of lactiferous duct and epidermis. Cheatle [3] believes that the

[1] Muir, R., *Brit. J. Surg*, 1935, 22, 728.
[2] Inglis, K., *Paget's Disease of the Nipple*, London, 1936.
[3] Cheatle and Cutler, *Tumours of the Breast*, 1931, London.

cells may arise in ducts or epidermis. The fact that Paget's disease may arise in other parts of the body does not help in solving the origin of the Paget cells because when it does so it most commonly affects skin rich in sweat glands. As the breast is a collection of modified sweat glands the anatomical and histological conditions are similar.

Two other conditions, closely allied to the true Paget's disease, must be mentioned. In one, a chronic inflammatory condition of the nipple and areola is followed by the development of a squamous-celled carcinoma, the process being in every way comparable to the development of carcinomata in other parts of the body in response to forms of chronic irritation. In the other, the eczematous condition of the nipple is secondary to a carcinoma of the breast, but is due to direct invasion of the surface epithelium by the cancer cells, and not to an intra-epidermic spread; in other words, the process is simply one of malignant ulceration (Fig. 183).

TUMOURS OF THE BREAST

The breast presents a rich field for the study of tumour-formations, for not only are a great variety of neoplasms encountered in it, but it is also subject to advanced reactive changes of a blastomatoid nature Our chief difficulty is in distinguishing between true benign blastomata and the very similar blastomatoid formations.

Innocent Tumours. Cysts of various kinds are quite common. Many of them are of inflammatory origin or due to the obstruction of a duct, but a number occur in the growth of neoplasms and will be referred to under the appropriate headings. Occasionally in retention cysts there are formed small overgrowths of the lining epithelium which project as papillomata into the cavity, and these may sometimes be regarded as true blastomata.

Simple benign tumours of the breast are not common The pure **fibroma** is a rare tumour, though in combination with epithelial elements the fibrous tissue neoplasms are among the most frequently seen of all the mammary new growths. It forms a firm rounded tumour, and often exhibits a considerable degree of myxomatous degeneration.

Myomata, lipomata, and **angeiomata** are all rare. **Myxomata** have been described, but most of them are probably degenerated fibromata.

Chondromata and **osteomata** are extremely rare.

Papillomata are usually quite small, they grow from the walls of the ducts, and may be multiple. They are composed of branching

connective-tissue processes covered by a layer of cubical or columnar epithelium.

Adenomata are more common. They occur, as a rule, as small nodular tumours consisting of tubules resembling the normal breast acini, surrounded by a varying amount of fibrous stroma. They may be recognised microscopically from the fact that the tubules are not arranged in lobules as in the normal gland, and from the absence of ducts.

Another variety is the **papillary cystadenoma** of the ducts. As its name implies, this tumour tends to produce cystic spaces which are filled, partly with a papillary ingrowth of the lining epithelium, and partly with a "colloid" secretion (Fig. 184). In between the cysts are areas of more solid growth consisting of irregular and folded acini. It may be a matter of extreme difficulty to discriminate microscopically between this tumour and an adenocarcinoma.

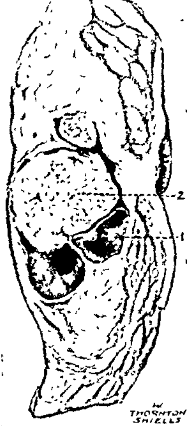

FIG. 184. Papillary cystadenoma of the breast. Some of the cysts contain "colloid" secretion (1), others are filled with a papillary ingrowth of the lining epithelium (2)

The commonest innocent tumour of the breast is the mixed epithelial and connective-tissue growth usually known as the **fibro-adenoma**. The name is a bad one since it implies that the adenomatous constituents of the tumour have the greater importance, and this is very rarely the case, for in the majority of tumours it is in the fibrous tissue that the greatest activity is seen, and the changes in the epithelium are secondary.

It would be more correct, therefore, to speak of adeno-fibromata, but the old name is so firmly established that little advantage, and some confusion, might result from any attempt to change.

The fibro-adenoma of the breast forms a firm lobulated tumour which is freely movable under the skin; several may be present in the same breast, and both organs may be affected simultaneously. The

majority of the tumours are small, but they may grow to an immense size. *Microscopically*, two varieties are recognised, the pericanalicular and the intracanalicular. In the pericanalicular form there is extreme proliferation of the connnective tissue around the tubules, so that each tubule becomes surrounded by a ring of fibrous tissue. In this way numerous small lobules are formed, and these are bound together by loose connective tissue, which also shows some hyperplasia. Frequently the periglandular zone shows a well-marked myxomatous degeneration. As one might expect, this variety of fibro-adenoma is dense and firm, and on section has a peculiarly granular appearance.

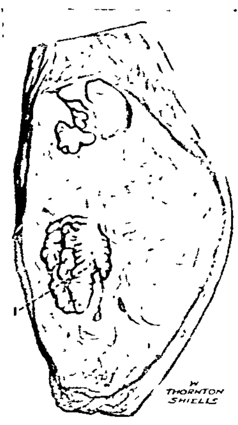

FIG. 185. Fibro-adenoma of the breast showing intra-cystic papillomata (1)

In the intracanalicular form the fibrous tissue growth is more diffuse, and the tubules become drawn out and distorted. In this way large cystic spaces, lined with epithelium, are produced, and these tend to become filled with a papillomatous ingrowth of the connective tissue covered by epithelium (Fig. 185).

Occasionally this form of fibro-adenoma grows to an enormous size, when it is known as "Brodie's sero-cystic sarcoma" (Fig. 186). It is unusually cellular, with a myxomatous change in the stroma, and the cysts and their contents are extremely complex. The majority of these tumours are perfectly innocent, but sometimes the connective tissue may assume sarcomatous characters.

Malignant Tumours. Sarcomata. As compared with the carcinomata, the sarcomata of the breast are distinctly rare. Solid and cystic forms occur, the latter closely resembling the cystic fibro-adenomata, or Brodie's tumours, already referred to. **Fibrosarcomata** usually form massive tumours having a comparatively low grade of malignancy. They are very liable to myxomatous degeneration and hæmorrhage, and pseudocysts may be produced in this way. **Round-celled** and **polymorphic** or **giant-celled sarcomata** also occur; they are more

malignant than the fibrosarcomata, and may exhibit a diffuse infiltrative growth.

Endotheliomata. An angeiosarcoma or perithelioma has been

FIG 186 Sero-cystic sarcoma, "Brodie's tumour," of the breast. At A the skin has become ulcerated from pressure.

described, but the majority of tumours described as endotheliomata are in reality anaplastic carcinomata

Mixed tumours consisting of connective tissue cartilage and bone with cysts lined by squamous or columnar epithelium are not uncommon in bitches and have been described in women. There is doubt as to whether they should be regarded as teratomata or fibroadenomata

with stromal metaplasia. The majority of these tumours are benign, but a few have been observed with metastases showing both types of tissue.

Carcinoma of the breast is extremely common in women between the fortieth and sixtieth years, and nearly one-sixth of the total deaths in females from malignant disease are due to it.

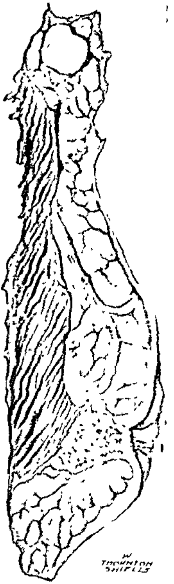

Fig 187 Scirrhous carcinoma of the breast, showing retraction of the nipple (1) and secondary deposits in the axillary glands.

Mammary carcinomata may originate in any part of the gland, though the most common situation is the upper and outer quadrant. The breast may previously have been healthy, but very frequently it shows fairly advanced lobular adenomatous hyperplasia.

The size and consistence of the tumours are variable, depending on the nature of the growth and the amount and character of the stroma. The commonest type, the scirrhous cancer, forms a small nodular tumour with an irregular outline; it is extremely hard, and on section has a peculiar "woody" appearance, often likened to an unripe pear (Fig. 187). Another variety, the encephaloid carcinoma, forms a rounded, considerably larger tumour of a softer consistence (Fig. 188). Degenerative changes are common in this type, and its cut surface may be studded with small points of necrosis, remarkably like tiny abscesses. Occasionally a tumour may exhibit such marked mucoid degeneration that the term "colloid carcinoma" is applied to it. Another type, the duct carcinoma, is a softish, rounded tumour arising beneath the nipple in relation to one of the lactiferous ducts. Sometimes the growth instead of being circumscribed is diffuse, and may exhibit an irregular formation of cysts. Finally, carcinomata may start in connection with simple cysts, either as nodular growths in their walls, or as intracystic papillomata.

Histologically, the growth is usually a carcinoma simplex, either of

the scirrhous or the encephaloid type. The scirrhous growth consists of solid trabeculæ of polygonal cells separated by much fibrous tissue which towards the centre of the growth is usually hyaline. Around the ducts of the breast there is great degeneration of the elastic tissue

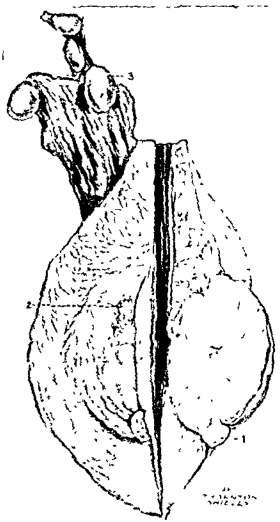

FIG. 188. Encephaloid carcinomata of the breast. The nipple (1) is pressed to one side, and the skin is ulcerated (2). There are secondary deposits in the axillary glands (3).

which is seen naked eye as white flecks (the " woody bits "). In the less scirrhous forms it is usual to find tubules lined by cubical epithelium. The encephaloid forms show very scanty fibrous tissue and the cells are usually polygonal and as seen in histological sections arranged in solid sheets.

Adenocarcinomata are also fairly common and so are forms intermediate between the two. Adenocarcinomata are commonly slow growing and bulky and remain circumscribed for a long time and metastasise late.

Duct carcinomata are of two types, the intra-duct or cyst papillary type and the type in which the growth arises in the duct epithelium and spreads along either completely or almost completely filling ducts. So that in sections rounded fairly well circumscribed masses appear and in places clearly in ducts, in one or more places infiltration will be apparent (comedo-carcinoma). The malignant papilliferous cyst-adenoma is a rare growth.

The growth and dissemination of mammary carcinomata are matters of extreme interest, for on a proper understanding of them depends the *possibility of successful operative treatment*. As *Handley has demonstrated*, dissemination may take place by a process of lymphatic permeation, but embolism plays a more important part and is responsible for most of the cutaneous, lymphatic, intrathoracic, and abdominal metastases. The general nature of the process has already been discussed (p. 17) In few other varieties of malignant growth are the metastatic tumours so numerous or so widely spread, and it is interesting to note that carcinomata of the breast share with similar tumours of the thyroid and the prostate the peculiarity of forming secondary growths in bones more frequently than most other neoplasm.

With the possible exception of the uterus, multiple tumours are more common in the breast than in any other organ.

Innocent fibro-adenomata or lobular adenomatous hyperplasia are frequently seen in association with carcinomata, while multiple benign tumours may show a considerable variation in their structure.

Primary multiple carcinomata have been described, though it is always difficult to establish beyond all possible doubt a separate origin for the different tumours.

A very few cases of the simultaneous growth of carcinoma and sarcoma have been recorded, but in none of them was there any very clear evidence that either tumour had any etiological relationship to the other. One might be prepared for the development of a sarcoma in the stroma of a chronic carcinoma, but this has not yet been demonstrated; indeed, in a case of combined carcinoma and sarcoma which Kettle recorded,[1] the sarcoma appeared to be the primary tumour.

[1] Kettle, E. H., *Lancet*, 1912, **2**, 750.

THE DUCTLESS GLANDS

THE THYROID GLAND

Innocent Tumours. Adenoma. Localised or general enlargement of the thyroid is a very common condition, and it is a matter of the greatest difficulty to distinguish between simple reactive hyperplasias and true blastomatous formations. Formerly it was held that the majority of thyroid nodules both colloidal and hyperplastic were simple tumours, yet the modern view is that true adenomata are uncommon and that the so-called adenomata are in reality nodules of hyperplastic or involuted thyroid tissue which have developed in association with varying stages of activity of the glands and have become demarcated as the result of secondary changes.

On the other hand, the **fœtal adenomata** may be regarded as true tumours. They are circumscribed pink or white nodules of variable size lying in a relatively normal thyroid. If adenomata are of any size they may undergo degenerative changes—hæmorrhage, hyalinisation of the stroma and calcification.

Microscopically the fœtal adenomata consist of minute closely set follicles containing little colloid, a tubular pattern or solid cords of thyroid cells. A peculiar adenoma is the Hürthle cell tumour ; this tumour consists of large polyhedral cells with an abundant acidophil cytoplasm and the cells are arranged in trabeculæ or small acini.

Innocent connective-tissue tumours of the thyroid are rare ; **fibromata, angeiomata, chondromata,** and **osteomata** have been described.

Malignant Tumours. Sarcomata are rare, but occur as highly malignant growths which spread rapidly to the tissues of the neck. They are usually of the **round-, spindle-, giant- or polymorphic-celled** type, and highly vascular forms, known as **angeiosarcomata** or peritheliomata, are also described.

Carcinomata are much less rare ; they are prone to develop in previously enlarged organs. The morphogenesis of thyroid carcinomata have not been studied with so much thoroughness as many other tumours, and very conflicting statements have been made with regard to them. Some forms appear to be extremely malignant, spreading to the tissues of the neck at an early stage, and giving rise to distant metastases, especially in the bones ; other varieties grow much more slowly and show little tendency to dissemination.

The *microscopical* structure of the tumours is equally variable

(Fig. 190). In some cases the growth can only be distinguished histologically from a simple thyroid adenoma by the demonstration of an infiltrative growth or secondary deposits. In these cases the tumour and its metastases produce colloid, and are to some extent capable of performing the functions of the normal gland. Another variety of tumour contains no colloid, but has the structure of a *glandular or simple carcinoma, and in the absence of any of the*

FIG. [illegible] The structure is that [illegible] some of [illegible] At the

Obj 16 mm. apochrom. Comp. oc. 6. Tube length, 160 mm.

characteristic features of the thyroid it may be impossible to prove that it originated in the gland, though the naked-eye appearances may strongly suggest such a source.

Instances have been recorded of the occurrence of combined carcinomata and sarcomata of the thyroid; indeed, such mixed tumours are said to be more common here than in any other organ. It must be remembered, however, that the histology of thyroid tumours, especially the rapidly growing ones, may be most complex. Occasionally the tubular structure may be entirely absent throughout the greater part of the growth, and, as the result of compression, the

cells may assume a distinctly sarcomatous appearance. These tumours are often extremely puzzling, and it is only by an examination of several sections taken from different parts that a true conception of their nature can be obtained (p. 190). A reticulin impregnation method is

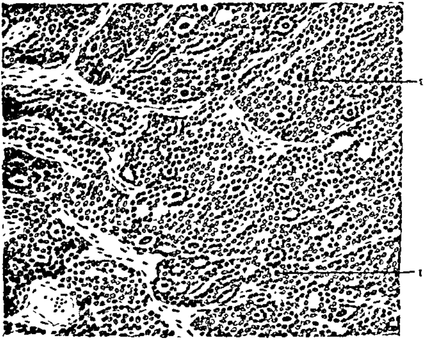

FIG. 190. Microscopic section of a carcinoma of the thyroid. The tumour is composed of large masses of cuboidal cells which occasionally form colloid-containing acini (t) supported by a scanty connective stroma.

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of great value in the analysis of obscure anaplastic growths as it usually facilitates the distinction between stroma and parenchyma.

It is worthy of notice that many thyroid tumours are exceedingly vascular, so much so that they may actually form pulsating tumours.

THE PARATHYROIDS

Tumours[1] of parathyroids are mostly benign and the commonest are adenomata. Their histological appearance usually closely resembles that of a normal gland, but in some only one type of cell is present. They may produce an internal secretion and be associated with osteitis fibrosa, or there may be no evidence whatever of their having had any

[1] Hunter, D., *Quart. Journ. Med.*, 1926–27, 20, 123; Hadfield, *J. Path. and Bact.*, 1932, 35, 259; Hunter, D. and Turnbull, H. M., *Brit. J. Surg.*, 1931–32, 19, 203.

functional activity. (Osteitis fibrosa may result from hyperplasia of the glands in the absence of tumour formation.) Again, either with hyperplasia or adenoma there may be an association with chronic renal disease (renal rickets). Carcinoma of the parathyroid[1] is not usually associated with skeletal changes.

THE THYMUS

There is still doubt as to the exact histiogenesis of the thymus whether the lymphocyte-like cells are true lymphocytes or primitive epithelial cells, but there is no doubt that it is a lympho-epithelial organ and its oncology supports this.

Innocent Tumours—fibroma, lipoma, lymphangeioma and teratomata (dermoids) have been described.

Malignant Tumours. Primary malignant tumours are usually lymphoepitheliomata. They form firm masses in the anterior mediastinum with considerable tendency to local infiltration and involvement of cervical lymph nodes. Microscopically they vary from quite well differentiated carcinoma to extremely anaplastic lymphoepithelioma.[2] **Lymphosarcomata** and other forms of reticulo-sarcomata are sometimes found. Carcinomata of the thymus[3] are sometimes associated with pluriglandular disturbance.

THE SUPRARENAL GLAND

Developmentally, the suprarenal gland has a double origin, the medulla being derived from the sympathetic nervous system, while the cortex is formed from the mesodermal cells covering the Wolffian body We see a corresponding difference in the blastomata of the cortex and the medulla.

Innocent Tumours. Adenomata. A nodular or adenomatous hypertrophy, in which the suprarenal cortex is studded with little spherical tumours of a yellowish colour, is quite common, and true adenomata are not infrequently seen They are usually small tumours, and resemble in their structure the zona fasciculata of the normal cortex.

Innocent **gliomata** and **ganglioneuromata** are rare tumours occurring

[1] Hall, E M, and Chaffin L., *West J. of Surg*, 1934, **42**, 578.
[2] Wu, T T, *J Path. and Bact*, 1935, **41**, 351
[3] Leyton O, Turnbull, H M, and Bratton, A. B, *J. Path. and Bact*, 1931, **34**, 635.

in the medulla. Other benign neoplasms which have been described are **lipomata** and **angeiomata.**

Malignant Tumours. Primary malignant tumours of the suprarenal, though somewhat rare, are of very great interest.

Tumours of Nervous Tissue may grow from the medulla. They occur chiefly in children, and are usually of the neuroblastomatous variety, but all the variants of sympathetic tumours may occur (see p. 169); they are peculiarly liable to form metastases in the skull bones. Another group of sarcomata are derived from the nervous elements of the medulla. They are usually described as gliosarcomata, but it seems probable that they are really neuroblastomata. They occur in children, and may be bilateral.

Phæochromocytomata [1] (chromaffinoma, paraganglioma), both innocent and malignant, are derived from the chromaffin cells of the medulla. They are extremely rare, but are of importance in that they may show functional activity secreting adrenalin and inducing periodic hypertension. The tumours are seldom large and are yellowish or white in colour. Microscopically they consist of closely set granular polygonal cells resembling normal medullary cells and staining brown with chrome salts.

Melanomata have also been recorded.

Carcinomata. Malignant epithelial tumours of the suprarenal are not particularly common, though they occur both in children and adults. They are derived from the cortex of the gland, and have a structure resembling adrenal cortex, or of atypical spheroidal-celled carcinomata. In children they have a remarkable effect upon the general physiology of the body, being almost invariably associated with precocious development of the reproductive glands and the secondary sexual characters and virilism in females. This syndrome may develop in association with cortical hyperplasia, cortical adenoma or carcinoma, but Vines has shown that in all cases the cortical cells show an affinity for acid-fuchsin when stained by a suitable method. Some cases of cortical carcinoma have shown the clinical features of Cushing's basophilism rather than the adrenogenital syndrome, but the distinction between these two conditions is as yet not clear.[2]

Secondary carcinoma in the adrenal is very common in carcinomata of the bronchus and much less common in melanotic and other carcinomata.

[1] Edward, D. G. H., *J. Path. and Bact.*, 1937, 45, 391.
[2] Broster, L. R., *B.M.J.*, 1940, 1, 425

THE PITUITARY GLAND

Tumours of the pituitary gland are chiefly of interest from the endocrinological symptoms with which they are associated. They are almost all benign and seldom very big.

Innocent Tumours. Primary tumours of the posterior lobe are almost unknown and the most important benign tumour is the adenoma of which there are three varieties corresponding to the cell types normally present in the anterior lobe.

Chromophobe adenomata are the commonest variety and have no hormonal activity, but produce their effects by compression of adjacent structures They may only be visual disturbances, but in children there is often a state of adiposity and infantilism (Fröhlich's syndrome). Although often confined within the sella turcica they may extend some way beyond the sella without any true signs of malignancy.[1] Microscopically they consist of acini of closely set polygonal cells with a granular cytoplasm ; occasionally they show a papillary structure.

Acidophil adenomata are seldom as large as the chromophobe type and are associated with gigantism in the child or acromegaly in the adult. Microscopically they vary, in some cases consisting entirely of acidophil cells, in others a mixture of mature and immature acidophil cells.

Basophil adenomata are often so minute that they can only be discovered by serial sectioning of the pituitary yet their presence is associated with Cushing's syndrome or hirsutism, obesity, hypertension and metabolic disturbance. In all cases of basophil adenoma and also in those cases of Cushing's syndrome associated with adrenal or thymic tumour, the basophil cells show a hyaline change in their cytoplasm.[2]

Craniopharyngioma (Cyst of Rathke's pouch). These tumours, which are usually cystic, are derived from the remnant of the craniopharyngeal duct They may be of considerable size and may invade the third ventricle. Macroscopically they are cystic with white solid portions which may contain calcareous material or bone ; the cyst fluid is brownish from altered blood and often contains cholesterol crystals. Microscopically they are lined with squamous epithelium on a framework of collagen. The epithelium may form sheets and on occasion the basal cells may be columnar, giving rise to an appearance suggestive of enameloblasts on which account they have often been misnamed

[1] Jefferson, G , *Proc Roy Soc. Med* , 1940, **33**, 433
[2] Crooke, A C., *J. Path. and Bact.*, 1935, **41**, 339.

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Malignant tumours are rare, but are usually carcinomata.

Secondary growths may arise by direct extension through the skull or from emboli.

ADENOMATA AND SECRETION

Hypertrophy and hyperplasia of the active cells of a ductless gland are always associated with hypersecretion, but adenomata may or may not be active. This is clearly shown by cases in which histologically identical adenomata are found, and in one there are signs and symptoms attributable to hormonal activity and in others no such signs. This fact further emphasises the autonomy of tumour growth.

Tumours which may be found in patients showing atypical hormonal activity are :—

Hyperthyroidism	Cellular adenoma of thyroid
Gigantism and acromegaly	Adenoma (usually acidophil) of pituitary
Cushing's syndrome	Basophil adenoma of pituitary
Generalised osteitis fibrosa	Adenoma of parathyroid
Virilism	Adenoma of adrenal cortex
Virilism	Arrhenoblastoma of ovary
Hypertension	Phæochromocytoma of adrenal
Hypoglycæmia	Adenoma of islets of Langerhans

THE CAROTID BODY

From the carotid body is developed a well-recognised tumour, often known as a "**potato tumour**," but as yet there is no certain agreement as to the exact histogenesis of the carotid body itself. It is clearly a neurovascular body and has some affinities with the glomus, but there is little evidence to support the view that it is formed of chromaffin tissue.[1] The tumour is derived from the specific cells of the gland. It forms an irregular oval body of a firm consistence and a yellowish colour. Bilateral tumours have been described.[2] It possesses only a low degree of malignancy, and seldom forms metastases.

Histologically, the tumour is composed of large spheroidal cells, which are grouped together in solid alveoli between a system of widely

[1] Russell, H., *Edin. Med Journ*, 1942, **49**, 366.
[2] Chuse, W. H., *J. Path. and Bact*, 1933, **36**, 1

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act., 1933, 36, 1.

dilated capillary blood vessels and is rich in medullated and non-medullated nerve fibres (Fig. 191).

Fig 191 Microscopic section of a carotid body tumour. The tumour consists of alveoli of spheroidal cells (1) lying among dilated thin walled capillaries (2) Obj 16 mm apochrom Comp oc. 6 Tube length, 160 mm

Gland of the Ductus Arteriosus. Bodies similar to the carotid body are found close to the ductus arteriosus and may well be the seat of tumours similar to those arising in that body.

THE COCCYGEAL BODY

Very little is known about the tumours of the coccygeal body, though Masson regards it as an arteriovenous anastomosis and a glomus type tumour has been described in relation to it.

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